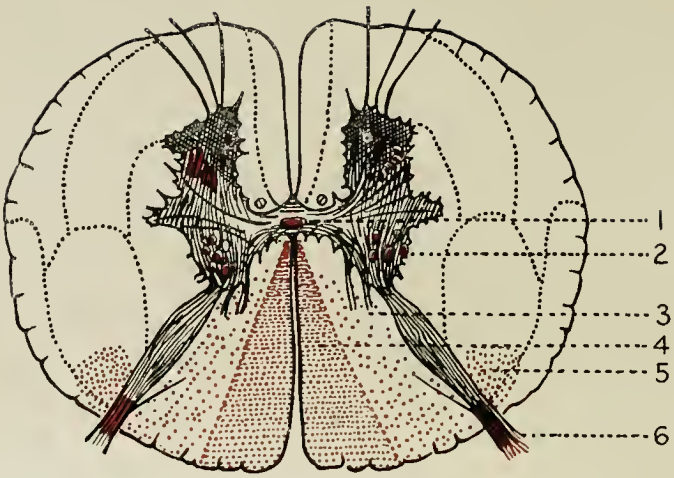
PELLAGRA



Diagrammatic cross section of the spinal cord of a pellagrin, the parts in red representing the lesions. 1, central canal; 2, column of Clarke; 3, tract of Burdach; 4, tract of Goll; 5, tract of de Lissauer; 6, posterior roots. (Procupiu, after Babes.) See page 145.

SOUTHERN MEDICINE

PELLAGRA

HISTORY, DISTRIBUTION, DIAGNOSIS, PROGNOSIS, TREATMENT, ETIOLOGY

BY

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To that long line of Physicians and Scientists from Casal through Lombroso to Sambon, and those who shall come after them who have been and are and shall be students of Pellagra,

THIS VOLUME IS DEDICATED BY THE AUTHOR,

with the hope that the day is not far distant when there shall arise from among them one to whom shall be revealed with clear and certain proof the true cause of the Mal de la Rosa.

PREFACE.

This is a book on Pellagra for the student and the practicing physician. It is not merely a discussion of Pellagra, nor is it devoted to upholding any special theory of etiology.

At the present time it is impossible to have a book of this size contain the entire data concerning the disease. It is not only impossible to include all such matter, but it would be also useless. We need the essential facts of the subject—we need to know its pathology, its diagnosis, and its treatment. There has been entirely too much speculation on Pellagra, and entirely too little investigation of Pellagra.

It is a pleasure to express my thanks to all those who have studied and written extensively on the disease. Among these are Casal, the elder Strambio, Jansen, Frapolli, Lombroso, Roussel, Hirsch, Sambon, Marie, and the contributors to the National Pellagra Congress of 1910. Other acknowledgments are made throughout the book. I wish to thank Dr. Eugenio Bravetta, of Mombello, province of Milan, for many photographs, and especially for his aid in the study of his pathological sections, for the preparation of which he deserves much credit.

I am particularly indebted to Dr. E. M. Green, clinical director of the Georgia State Asylum for Insane at Milledgeville, for permission to use his valuable work and classification on "Psychoses Accompanying Pellagra," and to Dr. S. S. Hindman, pathologist to the same institution, for permission to use his report on the cerebrospinal fluid.

The chapter on Alimentary Tract in Pellagra includes the researches of Dr. J. Clarence Johnson, of Atlanta, on the digestive system, and I wish to acknowledge my thanks to him for his aid in the preparation of this chapter.

My thanks are due to Dr. Charles C. Bass, of New Orleans, for photographs, and to Dr. J. O. Elrod, of Forsyth, Georgia, and to many others for valuable aid. Mrs. M. L. Ragin, my secretary,

has been of much assistance in the preparation of the manuscript and the index.

Finally, I wish to express my gratitude to one whose mature wisdom and kindly approval are always a source of constant help and encouragement.

STEWART R. ROBERTS.

ATLANTA, GA., May, 1912.

WORDS OF GOETHE.

The following, written by the poet Goethe in his "Italian Journeys" (from Brenner, in the Tyrol, Austria, to Verona, Italy), September, 1786, is of peculiar interest in connection with the now supposed etiology of Pellagra:

I know little, if anything, pleasing to say about the people. As soon as the sun rose over the Brenner paths in the Alps I noticed a decided change in their appearance, and especially displeasing to me was the brownish tan color of the women. Their features indicated misery, and the children were just as pitiful to behold; the men are little better, though their general features were regular and good.

I believe the cause of this sickly condition is found in the continued use of Turkish and heath corn. The people call the Turkish corn also yellow grain and the heath corn black grain. These are ground, the meal mixed with water, cooked to a thick paste, and eaten in this condition. The Germans across the Alps divide the dough into small pieces and fry it in butter. The Tyrolese, on the other hand, eat it plain, sometimes with cheese on it, but eat no meat the entire year; besides this, they eat fruit and green beans, which they soak in water and cook with garlic and oil.

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PELLAGRA

CHAPTER I.

GENERAL CONSIDERATIONS.

The manifestations of pellagra are definite only in wide limits. One case may be as different from another case as if each were a different disease. It is well, therefore, for the student of pellagra to note the varying and different symptoms of several typical cases, each case differing in course and severity from the others.

PRONUNCIATION.

Pellagra is pronounced in the United States in three ways. It is called (1) pĕl′lă-grä—*e* short as in fell, first *a* short as in am, second *a* broad as in father, with the accent on the first syllable; (2) pel-lā′grā—each *a* long as in fate, with the accent on the second syllable; (3) pel-lä′grä—each *a* broad as in father, with the accent on the second syllable. Dictionaries are presumably correct, but even they differ in the pronunciation of this word. It is an Italian word, originated among the common people of Italy, and was first used in medical literature by Frapolli in 1771 in the phrase, "*morbus vulgo pellagra*," meaning "a disease among the people called pellagra." The name is therefore of peasant origin, and is a union of two Italian words—pelle, meaning skin; agro, meaning rough. The final *e* before another vowel is dropped, the final *o* of agro is changed to *a;* thus pelle agro becomes pell + agra, or the present word pellagra, meaning rough skin.

In the Italian language the word is pronounced pĕl-lä′grä, each syllable separately and distinctly spoken, the accent on the second syllable, and each *a* pronounced broad as in father. This Italian pronunciation differs from all three used in America in that the Italians use *l* separately in the first two syllables, while in America the word is pronounced as if it were spelled with only one *l*. It is manifestly out of the question to pronounce it as the Italians do, and therefore the word has been Anglicized and is now an English word, and to be pronounced according to English methods.

Webster gives pĕ-lā′grä, but prefers pe-lă′grä; the Century dictionary gives only one pronunciation—pe-lā′-grä. Webster's preferable pronunciation is not used at all in this country, and, since both dictionaries give pĕ-lā′grä, and, in addition, the other two related words—pellā′grin and pellā′grous—are pronounced with the *a* long and accented second syllable, as pĕ-lā′grin and pĕ-lā′grus, it seems wise to use this altogether natural and easy American pronunciation, pĕ-lā′grä.

TYPICAL CASES.

One need not expect to find a typical pellagra. It is a disease of many symptoms and of many variations; its only consistency is its inconsistency; it seems cured and yet recurs; the pellagrin seems to be approaching his end and yet lives for many years; it spreads and is not contagious; the offspring of the pellagrin receives his mark and yet it is not inheritable; it is not and appears; it is and disappears; it is a morbid entity and yet it contains within itself many lesser morbid entities; it falls with equal right in the sphere of dermatology, neurology, and gastrology, and yet it is a general disease; divers diseases become one, and this one is called pellagra; there is no pellagra—only the pellagrous.

The following cases are selected with a view of illustrating different pictures of the same disease in reference to severity, marked improvement, early death, pellagra in the negro, termination in insanity, and general clinical symptoms common to pellagrins. It is well to understand and keep in mind the general picture of the disease, but it is well also to remember that this picture is a composite picture, made up of widely different and apparently unrelated pictures, imposed one upon the other in all imaginable angles, and each individual picture, as well as the composite result, varying in hue and aspect in each case and in every season. No disease is so plain as pellagra in the early spring, and no disease so obscure as pellagra in the same patient in midwinter; a slight indigestion may introduce the pellagrous attack, and the case be so slight in its systemic effect that a month later no apparent traces remain.

Case 1.

A housewife, aged 48, the mother of nine children, noticed that for the past month she had not been feeling as well as usual. Up

to this time she had always been an exceptionally healthy woman. She married at 17, lived in the mountains of North Georgia until grown, and has lived in the country all her life. She had always done her own work; her labors had been very easy and without complications; no miscarriages, and her menstrual period regular until the last period, which did not appear. Her husband is living, and her children are healthy.

About May 1st her appetite began to fail, and there gradually developed a feeling of uneasiness in the stomach, which at times amounted almost to nausea. There seemed to be an increased amount of gas in the intestines, although she did not belch at all. There was no pain in the abdomen or anywhere else, and she attributed her trouble to "biliousness and indigestion," but noticed that her indigestion seemed to continue, whether she ate or not. The uneasiness in the abdomen was neither made worse nor better by food. About this time a diarrhea began to develop, and she would have from four to eight thin stools daily, but did not pass any blood. These movements had a peculiar odor like oats or barley after soaking in water.

She did not feel very weak, but thought her clothes hung rather loosely, and imagined she was losing a little flesh. About this time she noticed a peculiar discoloration on the back of her hands, and thought at first they were sunburned, though she could not remember being in the sun long enough to have caused this. This color on her hands ended just above the wrists; it did not hurt her, though when she used hot water to wash the dishes her hands seemed tender and sensitive.

She had come very near having headache. She had strange feelings in her head, as if something were about to happen, and if she stood up quickly she felt slightly dizzy. Her husband thought she was rather nervous, and she cried easily for seemingly no reason.

On examination she gave one the impression of having great weariness, and seemed glad of an opportunity to lie down. The palms of her hands were normal, but on the backs the skin was of a deep sunburn, with a peculiar brown tint added. It was symmetrical on both hands, extended from above the wrists to about the middle of the fingers, and the skin over the first phalangeal joints was loose and unduly wrinkled. In the middle of the back of one hand the skin was beginning to peel off, leaving a thin new skin

beneath slightly lighter in color than the old. Her hands looked thin, and the fingers rather long drawn out. Her elbows were rough and the skin loose.

Her tongue was without a coat—red, with a few little fissures about the middle; the inside of the cheeks was red and tender, and her whole mouth sore. Heart and lungs negative; abdomen negative, except for the presence of large amount of gas in the intestines. Knee jerks equal and slightly exaggerated; eyes normal; no ataxia, no ankle clonus, or Babinski reflex. Pulse, 90; temperature, 98; respiration, 18. Urine averaged 30 ounces in twenty-four hours; specific gravity, 1.005; no albumen, sugar, or casts; a few blood and epithelial cells. Blood normal, except hemoglobin, 80 percent. Weight, 135.

She was put in bed for a few days, and then allowed to sit up

TABLE SHOWING THE VARYING CONDITIONS OF CASE 1.

Date.	Hour.	Temperature.	Pulse.	Respiration.	Date.	Hour.	Temperature.	Pulse.	Respiration.
June 6	11 a. m.	102	114	18	June 20	8 a. m.	98½	80	18
6	1 p. m.	101½	98	20	20	4 p. m.	98½	88	16
6	3 p. m.	102½	94	20	21	8 a. m.	98	80	20
6	6 p. m.	101	92	18	21	4 p. m.	98½	82	18
7	8 a. m.	100	90	20	22	8 a. m.	98	80	18
7	4 p. m.	99	94	26	22	4 p. m.	98½	78	18
8	8 a. m.	98½	90	18	23	8 a. m.	98	92	20
8	4 p. m.	99	82	24	23	4 p. m.	98½	72	18
9	8 a. m.	99	90	24	24	8 a. m.	98½	80	18
9	4 p. m.	98½	100	18	24	4 p. m.	99	99	20
10	8 a. m.	97½	78	18	25	8 a. m.	98½	100	22
10	4 p. m.	98½	92	14	25	4 p. m.	99½	100	20
11	8 a. m.	98	90	20	26	8 a. m.	98	98	16
11	4 p. m.	99	84	18	26	4 p. m.	98½	86	18
12	8 a. m.	99	80	20	27	8 a. m.	97½	82	16
12	4 p. m.	98½	86	14	27	4 p. m.	99½	86	16
13	8 a. m.	98	96	18	28	8 a. m.	98½	90	18
13	4 p. m.	98½	78	18	28	4 p. m.	99	76	20
14	8 a. m.	98	90	16	29	8 a. m.	98	82	16
14	4 p. m.	98½	86	16	29	4 p. m.	98½	92	16
15	8 a. m.	98½	100	16	30	8 a. m.	99½	80	16
15	4 p. m.	99½	88	16	30	4 p. m.	99	82	18
16	8 a. m.	98½	100	16	July 1	8 a. m.	99	88	16
16	4 p. m.	99	98	14	1	4 p. m.	99½	92	18
17	8 a. m.	98	88	14	2	8 a. m.	99	88	16
17	4 p. m.	98½	100	16	2	4 p. m.	99	84	18
18	8 a. m.	98½	80	20	3	8 a. m.	99½	88	18
18	4 p. m.	98	88	16	3	4 p. m.	99½	80	18
19	8 a. m.	98½	99	20	4	8 a. m.	98½	80	18
19	4 p. m.	99	83	18					

at intervals. Her diet was rather full, with the exception of pastries and heavier vegetables, and she was given milk and albumens between meals and at bedtime. Fowler's solution was given, beginning at 3 drops and increasing gradually to 10, three times a day. She was encouraged, and seemed better on the days her friends and relatives visited her. She grew better rapidly, gained in strength and flesh, and was discharged on the twenty-ninth day apparently in good health and with a gain of 8 pounds.

The interne at the hospital marked this case "cured" on the records, much to the displeasure of the head nurse. I heard a month later that the woman was improving, but had at times slight attacks of diarrhea.

Discussion of Case 1.

This case illustrates the first attack of pellagra in a previously healthy woman of middle age. Notice that she lived in the country, and that digestive disturbances ushered in the attack. Without the bilaterally symmetrical erythema, the diagnosis might have been incorrect. The nervous and cutaneous symptoms were subordinate to the digestive disturbances and the diarrhea. The pulse was fast and the temperature slightly below normal; the urine of low specific gravity. She lost flesh, seemed tired, and appreciated encouragement. The only medicine used was a form of arsenic.

Case 2.

A widow, aged 30, no children, complains of pains all over her body, and a diarrhea that comes every three months for about three days. Her pains are worst in the waist line. Her family history is negative. In childhood she had measles, whooping-cough, and chicken-pox. She had good health until her husband died in March, 1904, and grief over his death brought on an attack of nervous exhaustion. She had a similar attack three years later. In 1908 she was operated on for appendicitis and a movable right kidney double in size. This right kidney is still very sensitive. She felt bad in the spring of 1908 for two or three months, but improved after going to the mountains. This sensation of being weak and run down recurred in the springs of 1909 and 1910. She improved each time after going to the mountains, but now, August, 1910, there is a recurrence of these spring attacks, this one more severe than ever before.

She is constipated at the present time, sleeps poorly, and has a good appetite. Her menstrual period has been irregular, and has not appeared for the last three months. She has suffered two nervous breakdowns in the last six years, both of them occurring in the spring of the year. She is now very irritable and nervous. She is a highly educated woman, and was formerly in the habit of

TABLE SHOWING THE VARYING CONDITIONS OF CASE 2.

Date.	Hour.	Temperature.	Pulse.	Respiration.	Date.	Hour.	Temperature.	Pulse.	Respiration.
Sept. 22	8 a. m.	99	102	18	Oct. 8	12 m.	100½	126	24
22	4 p. m.	99	84	20	8	4 p. m.	101	132	24
23	8 a. m.	98	90	18	8	8 p. m.	102	134	26
23	4 p. m.	99	102	26	8	11 p. m.	101½	142	26
24	8 a. m.	98	98	24	9	3 a. m.	102½	140	28
24	4 p. m.	98	96	24	9	8 a. m.	101¼	132 [2]	26
25	8 a. m.	98	102	24	9	12 m.	100½	128	18
25	4 p. m.	98	70	26	9	4 p. m.	100	134	26
26	8 a. m.	98	90	20	9	8 p. m.	102	130	22
26	4 p. m.	99	102	20	9	10 p. m.	102	140	26
27	8 a. m.	99	108	20	10	2 a. m.	102½	120	22
27	4 p. m.	99	100	24	10	8 a. m.	100½	120	20
28	8 a. m.	98	100	24	10	12 m.	102	134	28
28	12 m.	99	108	16	10	4 p. m.	102	130	28
28	4 p. m.	99	100	18	10	8 p. m.	101½	134	26
29	8 a. m.	99	100	20	10	12 p. m.	102	126	26
29	4 p. m.	99	102	20	11	8 a. m.	101½	140	30
30	8 a. m.	98	100	20	11	12 m.	101	132	28
30	4 p. m.	99	108	20	11	4 p. m.	101	124	30
Oct. 1	8 a. m.	98	98	18	11	8 p. m.	102	120	30
1	4 p. m.	99	108	22	11	12 p. m.	101½	126	30
2	8 a. m.	99	130	20	12	2 a. m.	100½	120	30
2	4 p. m.	99	120	24	12	8 a. m.	98½	124	22
3	8 a. m.	99	126	24	12	12 m.	102	112	26
3	4 p. m.	100	130	24	12	4 p. m.	100½	120	28
4	8 a. m.	99	130	28	12	6 p. m.	103	130	34
4	4 p. m.	99½	120	26	12	10 p. m.	103	140	32
5	8 a. m.	101½	128	30	13	1 a. m.	103	140	19
5	4 p. m.	102	150	28	13	5 a. m.	104	140	20
6	8 a. m.	103	120	24	13	8 a. m.	104	...	22
6	4 p. m.	103	140 [1]	30	13	4 p. m.	103	128	24
7	8 a. m.	101	128	22	13	8 p. m.	103	140	28
7	10 a. m.	100½	120	26	13	12 p. m.	103½	140	32
7	4 p. m.	101½	150	26	14	2 a. m.	104½	...	22
7	7 p. m.	102	148	26	14	8 a. m.	103 [3]	130	28
8	1 a. m.	102½	128	22	14	12 m.	104	...	26
8	8 a. m.	101	120	20	14	9 p.m. [4]			

[1] Direct transfusion.
[2] Direct transfusion.
[3] Axilla.
[4] Patient expired.

reading a great deal. She has noticed a gradual failure in her memory and ability to understand what she reads. At present it is often necessary for her to read the same sentence or paragraph over two or three times before she can understand it, and she has difficulty in remembering even the simplest things.

Her weight three years ago was 100 pounds; now 86. She is a tired, nervous-looking woman, with little strength. She gives one the impression of exhaustion and rapidly approaching cachexia. On September 13, 1910, she is nervous and suffers with abdominal uneasiness from no apparent cause that she knows. The entire dorsum of both hands is rough, scaly, cracked in places, especially over the knuckles, and the dorsum of the wrists presents the same appearance, the whole area having a light-russet tint. Over the knuckles the soreness is more severe; a little serum exudes from the raw surface of the fissured skin, and above the erythematous area on the forearms the skin is rough up to and including the elbow on the extensor surface. This erythema and roughness is symmetrical on both sides.

Between the fingers on the back the brown tint changes to a pink or red, and the tips of the fingers on the palmar surface seem unusually pink and clean. The skin on the back seems to be peeling in places, and a skin lighter in color, but still pigmented, appears beneath. The skin of the erythematous area is rather glistening, thin, and dry, and scales are larger than the bran-like scales of the nonerythematous area above the wrist. The forehead is slightly rough, although not enough to be apparent without very close examination. There is some atrophy of the hands, and the skin is looser than normal.

The heart and lungs are negative; gas is present in large amounts in the intestines, and the abdomen has a peculiar appearance as if about to point at the umbilicus. She thinks her hands are swollen at times, especially after a restless, sleepless night. Her reflexes are all exaggerated; no ankle clonus or Babinski reflex. Her mind is noticeably slow and dull; it is an effort for her to answer a question at all; the introduction of a new subject causes an effort on her part to incorporate it into the stream of her consciousness, and she gives the impression of abject neurasthenia, with a tendency to melancholia.

Her height is 5 feet 1 inch. Pulse, 96; temperature, 99.5; urine, 1.005; acid, no albumen or sugar, and the microscope shows

nothing abnormal. Hemoglobin is 75; reds, 4,602,950; whites, 9,400. Stomach contents after test meal showed 190 cc., free HCl .15 percent; total acidity, .33 percent.

Fig. 1.—Pellagrous boy. Dermatitis on hands and face. Austrian case. (After Merk.)

The diagnosis is, of course, pellagra of possibly six years' duration. She is apparently in the stage of cachexia, and the outlook is bad. She became gradually worse; nausea, vomiting, and diarrhea increased, and pulse rose to 130; temperature, 99.3°. On

October 9th, four days before her death, examination of blood showed hemoglobin of 70 percent; reds, 2,780,000; whites, 6,970. Differential count: polynuclears, 57 percent; lymphocytes, small, 24 percent; large, 16 percent; eosinophiles, 3 percent. Her fever and pulse continued to rise, great quantities of bile-stained fluid were vomited, gas in the abdomen increased, abdomen distended, bowel movements of a quart of pure watery discharge. Dissolution on October 13th, with temperature in axilla of 104.3° just before death.

Discussion of Case 2.

This is a case of recurrence for six successive years, reaching finally cachexia, with rapid death. The trouble was not diagnosed until two months before her death. The erythema was present in August. The blood showed excess of lymphocytes. The mental symptoms were not as severe as one would have supposed from the physical condition. Rest, treatment, arsenic, and transfusion were of no avail. The rapidity of the pulse was out of all proportion to the temperature. During the last month the blood lost red corpuscles rapidly, but the hemoglobin remained nearly the same.

Case 3.

A married woman, aged 25, with one healthy child 3 years old, was seen on June 24, 1911. Her father died of paralysis at 56, and her mother is living and well, 52 years old. She has always lived within one hundred yards of a branch and half a mile of a creek all her life, and has eaten corn bread in usual amounts. For the past five years she has been especially nervous at her menstrual period, and she does not think her nervous system is in a good condition. During this time her health was bad every spring, extending even into midsummer. During these spring attacks she noticed she grew weak and had some dizzy feelings, but thought she had the "spring fever." During the spring of 1910, with the usual spring weakness, she had a slight stroke of paralysis; and her whole left side has been of little use in work since. Her menstrual period is regular, but scanty; no pain, except backache at times. She has never had any diarrhea, and is usually constipated. Lately there has been a feeling of dullness in her head, almost headache, and she grows despondent and cries at times.

There is evidence of a right hemiplegia, slight hemiplegic gait,

left knee jerk absent, and slight ankle clonus in left foot. Right knee jerk slightly exaggerated. Her usual weight is 135, but she has lost 8 pounds this spring. She looks weak, though well nourished. Her face is sad. Pulse, 90; temperature, 99.4; tongue slightly coated in middle, sore and red at tip and margins. Blood pressure, 85 mm. One month ago her mouth was sore and raw inside; gums and inside of lips still red; throat red. She has too much gas in the abdomen, though her appetite is good, and there has been no nausea. Three weeks ago the backs of her hands grew red, and she thought they were sunburned; the skin from the middle of the fingers to above the wrists then began to peel off in scales and at times she felt burning sensations in her hands and feet. Her hands now are rough and cracked slightly, of a sepia tint, the finger tips pink and clean. Blood shows hemoglobin 85 percent; urine with a specific gravity of 1.012, otherwise negative. Heart, lungs, and abdomen negative.

Discussion of Case 3.

This case illustrates a pellagra of probably five years' standing, no diarrhea, no nausea, and a slight hemiplegia, probably of pellagrous origin. This case might have been diagnosed as a chronic neurasthenic, and indeed I suspected neurasthenia, when I first saw her, from her general appearance. The erythema clinched the diagnosis of pellagra. There was no great inroad made on the general nutrition; even her periods continued. She had probably had the erythema before, though had never noticed it until this last attack. This type corresponds more to the chronic form common in Italy. Notice the burning in her hands and feet.

Case 4.

A farmer, aged 50, the son of pellagrins, was seen in August. He had an attack of pellagra in the spring of 1910, with a recurrence the following September. In the spring of 1911 there was a third attack, this time more severe than in the preceding year. Since March he seemed to grow worse rapidly. He lost 40 pounds; his memory became bad, and his mind almost a blank. He was brought to the hospital a month ago suffering with acute confusional insanity, difficulty in speech, cachectic, and helpless.

His tongue is without a coat, bald, red like a cut beet, and covered with small fissures. The erythema extends from the middle

of the second phalanx half way up the forearm to the elbow on the extensor surface, and around the wrist, meeting on the flexor surface. All this erythematous area is peeling and cracking; the hands are thin and bony; the fingers long and keen. Above the eruption the skin is rough and scaly; this roughness extends up on the shoulders, and even appears on the trunk, forehead, and as scaly patches below and behind each ear. Erythema on ankles, half way up leg to knee; knee rough and scaling. The elbows are exceedingly rough, almost like an ichthyosis. His lower legs somewhat spastic, and he is unable to control them. Before he became bedridden he was ataxic; would fall at times, and often stagger when walking.

His entire left side presented a striking contrast with the right. On the left he had ankle clonus, Babinski reflex, trophic disturbances of the left hand, fingers slightly swollen at the tips; the nails white, thick, long, and swelling at base and beneath, with contractures of fingers—a claw hand. Knee jerks greatly exaggerated, eyes glassy and staring.

He was put in bed and showed marked improvement from the beginning of treatment. He was fed four times daily, chiefly on meats, milk, cheese, salads, a few vegetables. He was given iron, quinin, and strychnin, Fowler's solution in increasing doses, and occasionally tincture of nux vomica. A month after treatment began he was growing stronger, had a good appetite, and could talk a little, though his ideas were still confused. He will probably continue to improve until next spring, though confirmed dementia may develop.

Discussion of Case 4.

This case illustrates the rapid onset of cachexia and insanity in a man; trophic changes in the hand; wide distribution of the rough skin; marked improvement after cachexia had begun; ataxia, and spastic condition of lower extremities. The spinal cord was, of course, markedly affected, and the nervous symptoms predominated. Diarrhea was almost absent, yet cachexia developed rapidly.

Case 5.

A negro woman, aged 52, after a week of rather unusual feebleness, beginning about May 1st, went to bed from sheer weakness. She had been healthy and strong, did her own housework and

washing, and weighed 172 pounds. At times everything seemed to swim before her eyes, and it seemed that her legs would give way under her when she stood or tried to walk. Her mouth was sore, her gums bled, tongue raw, and it even hurt her to swallow water. Diarrhea began and grew worse, and when she went to bed she noticed streaks of blood in the stools. Her hands and feet burned; she had pains in the left back along the middorsal region; and on account of a constant feeling of nausea and this rawness in her throat she ate hardly anything.

About May 10th she presented a characteristic roughness on the back of the fingers, hands, and extensor surfaces of forearms half way to elbows. On the back of the hands there were several blisters, varying in size from a pea to a quarter and containing serum, occasionally streaked with blood, with an ulcerated base. The dermatitis was symmetrical, and one could not help thinking that the skin was similar to a burn. The roughness was not the usual color of the pellagrous erythema, but presented somewhat the appearance of an old negro's hand on a cold winter morning. It seemed at certain angles of a dark, ashy gray, and as if the dry skin would shed off in scales if the hands were well washed in warm water. There were patches of dermatitis on each side of the nape of the neck, and at the base of the alæ of the nose. The ankles and shins were rough, and at times the feet and hands were slightly swollen. Her feet and hands burned severely at times.

Temperature rose to 103.5°, with pulse at 120. Her eyes had a staring, vacant expression, and she looked wild and anxious. Reflexes all exaggerated, and she lay in bed in a rather stuporous condition. Her mind rapidly failed her, and control was lost of the lower limbs. She seemed a mass of helplessness. Occasionally she grew rigid and half violent, and then relapsed into a stuporous condition. Her urine contained a trace of albumen, with a few hyalin and granular casts. Diarrhea continued until finally incontinence of urine and feces developed. Toward the close she developed opisthotonos, though most of the time she was rather quiet and rigid. She died on June 6th, with a temperature of 105, but the fever ranged from 101 to 104 after she went to bed. After death she looked as though she had lost forty or fifty pounds. The rapidity of the disease, its increasing severity until death, gave one the impression that the patient was suffering with an acute infectious disease. Diarrhea, temperature, high pulse, prostration, emaciation added evidence confirming this idea.

Discussion of Case 5.

This is typhoid pellagra, or the *tifo pellagroso* of the Italians. The eruption was a wet dermatitis, and the attack grew rapidly worse. Notice the tendency to muscular rigidity and opisthotonos. The kidneys were involved. Stomatitis and anorexia severe. The continued fever distinguished this form. Death in five weeks.

DEFINITION.

Pellagra is an endemic and epidemic disease, periodic and progressive in its course, and characterized by a series of symptoms involving chiefly the digestive, cutaneous, and nervous systems.

GENERAL DESCRIPTION.

Pellagra may be endemic in country communities for a century, as in Italy, or suddenly epidemic, as in America. It varies in length from the six weeks' course of typhoid pellagra to twenty or thirty years, or even longer, of the chronic forms. It finds its chief home in the country districts, and attacks all classes, all ages, and both sexes, but does not attack dwellers in crowded cities. The attack begins usually in the spring and summer months, recurring with increasing severity every spring. A second attack may occur in the late summer or autumn months, with remission of symptoms and improvement during the winter. Its onset is insidious, its attack is periodic, and its course is progressive. The symptoms of the digestive tract are stomatitis, œsophageal burning, pyrosis, gastralgia, belching, nausea, gastritis, enteritis, dyspepsia, diarrhea usually and constipation rarely. The chief cutaneous symptoms are a peculiar, bilaterally symmetrical erythema, with progressive desquamation and pigmentation, a branny roughness of symmetrical skin areas, occasional serous or bloody blisters, and trophic changes around the nails. The chief nerve symptoms are a chronic neurasthenia, exaggerated reflexes, vertigo, ataxia, spastic and paralytic gaits, palsies, and paralytic strokes; occasional ankle clonus and Babinski reflex. Mental symptoms include sadness, melancholia, dementia, mania, confusional insanity, mutism, murder, and suicide. Emaciation and chronicity go hand in hand. The diagnosis is generally easy, and the prognosis varies

with the type of the disease and the time treatment is begun. An early diagnosis is important.

IS PELLAGRA CONTAGIOUS?

Endemic and epidemic diseases spread by contagion or the conveyance of a disease from one person to another by direct contact, as illustrated by small-pox; by bacterial infection of one person by germs from another, as illustrated by the tubercular infection of a wife from a tubercular husband; by bacterial or protozoan infection through the bite of an insect which acts as host, as illustrated by malaria and yellow fever by different mosquitoes; by bacterial or parasitic infection through food and water, as illustrated by cholera and trichina spiralis; by parasites burrowing through the skin, as illustrated by scabies and uncinariasis. As the cause of one disease after another is discovered, the number of diseases officially classified and popularly called "contagious" continues to decrease. Yellow fever a short time ago was always and everywhere considered contagious, and a medical man who would have disputed the contagiousness of yellow fever would have been considered foolish indeed, yet yellow fever is not at all contagious and the criminal is a mosquito.

Applying this classification to the transmission of pellagra, two facts are clearly apparent—(1) pellagra is not transmissible by contagion from one person to another; (2) pellagra is not transmissible by infection from one person to another. It is neither contagious from person to person, as smallpox, or infectious from person to person, as tuberculosis. In certain quarters there is objection to the use of the word contagious, but, until the real cause of every disease is discovered, this word is needed. The truth of these two propositions denying the transmissibility of pellagra is amply proved by the following facts:

1. The limitation of pellagra to the rural population. People who live in cities need have no fear of the disease, because pellagra stops at the city gates. Paved streets, high buildings, and crowded populations are not its home. This is one of the outstanding facts of the disease. Because pellagra develops in villages and towns of a few hundred or a few thousand inhabitants does not contradict the immunity of cities. Especially in the southern states these villages are under the same condition of living and environment

as far out in the country. An investigation of many of these so-called city cases will reveal the fact that they contracted the disease in the country, or spent much of their time in rural districts.

2. The limitation of the disease in many cases to large families or to several families living together under the same conditions of daily life. Alessandrini found 269 Italian families of 1,659 persons, and only 274 pellagrins among them, and of these only five families had 2 pellagrins each. One family of 21 members and another of 13 had only one pellagrin in each.

3. The complete immunity of hospitals, asylums, orphan homes, hotels, summer resorts, and all institutions where pellagrins are admitted for temporary or permanent residence. Nurses and attendants who stay with pellagrins all the time, physicians who treat them, relatives who live and sleep with them, are all alike immune. At the pellagrosari in Inzago, Mogliano Veneto, and Rovereto, where thousands of cases have been treated, no physician, nurse, or attendant has ever developed the disease.

4. The enormous intercommunication between urban and rural populations, and the absolute failure in any instance of pellagra to develop along the highways and lines of travel, or in cities where exposure in pellagra countries is constant.

5. It is impossible to reproduce the disease by inoculation from the serum exuded from the skin or from the blood and saliva of pellagrins. It is impossible to convey the disease from pellagrous wet-nurses to suckling infants in lactation. Here the very food of the infant is secreted from the blood of a pellagrin, and yet there is no record of the transmission of the disease to the infant. Sambon quotes Nardi in a conclusive way: "Although several children belonging to the upper classes of this town (Milan) were suckled by women recognized to be pellagrins at the end of lactation, nevertheless, notwithstanding that some of the nurslings have now passed their fifteenth year of age, not one of them exhibits any sign of having contracted the nurse's disease." I know of no better way to test the contagiousness of the disease than this, and especially since these cases were observed for a period of fifteen years. It is a common observation in medicine that nursing infants are easily affected by a disease or even passing illness of the mother, and the susceptibility of infants to contagious diseases is well known. The contagiousness decreases with age, as illustrated by

scarlet fever and mumps, and, if there is a remote possibility of contagion in pellagra, it should appear in infants nursing pellagrous milk, and the development of the disease would not be long delayed. It did not develop in such nurslings either during infancy or thereafter.

6. In the surgical procedure required for the transfusion of blood from a healthy donor into a pellagrin in the last stages of the disease, open wounds in both are brought in contact, vessel is joined to vessel, and for periods exceeding an hour. The disease is at its height, and, if either contagion or infection were possible, it would be at this time, and yet there has been no development of pellagra in any donor.

In the country districts in Italy and in America there is unquestionably an uncertainty of belief regarding contagion, and a suspicion in areas where the disease develops with great rapidity that it is somehow contagious. In an area of less than one-half mile in length along the banks of a small branch and pond near Forsyth, Monroe county, Georgia, 5 cases of pellagra originated. Elrod, of Forsyth, who drove me out to this endemic area, called my attention to the fact that there were no cases between these and the town of Forsyth, nine miles away, and how easy it would be to believe in the contagiousness of the disease if one merely viewed these 5 cases. It is easy in the popular mind to believe that, if a disease spreads in a community, it is therefore contagious, but the medical mind knows how false is this assumption. Pellagra does spread in one of its endemic areas, not because it is contagious, but because the people live in this area under the same conditions and are subject to the same causes of the disease. The point is that a pellagrin can not convey the disease by removing to a nonendemic area, but a well person can contract the disease by moving into an endemic area.

It is important that this matter be understood, and the fears of relatives and friends of pellagrins be allayed. I have known a young lady to develop the disease, her friends to forsake her, and her relatives to appear only when necessary and in plain fear of the patient lest they contract the disease from her. Pellagra is bad enough, and the sadness symptomatic of the disease is sufficient, without causing the pellagrin to feel that she is a menace and a source of contagion. It would be different if it were true, but pellagra is not contagious.

WHICH SEX IS MORE AFFECTED?

More women than men suffer with pellagra. This is one of the striking features of the disease. A study of groups of cases reported by general practitioners in America reveals the constant preponderance of female pellagrins. A few of these taken at random follow:

Seven cases, 5 women and 2 men; 24 cases, 14 women and 10 men; 9 cases, 8 women and 1 man; 10 cases, 7 women and 3 men; 18 cases, 13 women and 5 men; or of these five groups, with a total of 68 cases, 49 were women and 19 men. The following groups from the American asylums for the insane report somewhat the same proportion: of Zeller's 130 cases from Illinois, 75 were women and 55 men; the Cook county institutions in the same state report 26 cases, with 13 of each sex; the East Mississippi Asylum reports 9 cases, 7 women and 2 men; in the Florida Hospital for the Insane, among 85 women there were 11 pellagrins, and among 240 men only 2 pellagrins. Along the foothills of the Alps in Umbria, Italy, Alessandrini found in one area 254 pellagrins, 192 women and 62 men. In Roumania, of 19,796 cases 9,132 were men and 10,664 were women.

Warnock's report from the Egyptian government hospital for the insane for the nine years from 1901 to 1909 inclusive gives 636 pellagrous admissions, and of these 477 were men with 69 deaths, and 159 were women with 24 deaths. The figures of both Sandwith and Warnock seem to prove that in Egypt at least there are more men than women affected, but their figures are from hospital and asylum sources. In Italy, in 1847, out of 1,503 pellagrins in Venice and Piedmont, 658 were men and 854 women, a proportion of 4 to 5; another group of Italian statistics gives 2,289 men and 2,478 women. Dr. Fritz, at Inzago, in the province of Milan, after an experience of thirty years with the disease believes women always suffer more than men. The proportion of male to female cases in the United States is from 1 to 4 to 3 to 4, depending on the locality; the average is probably about 2 to 4, as illustrated by Porter's Florida figures of 33 men and 41 women. Grimm found 111 females and 29 males in three Kentucky counties; and of 189 deaths from pellagra in Texas, 153 were females and 36 males.

Nowhere have I found any adequate explanation of the excess of pellagra in women. In Italy it is said that more women have

pellagra because they work in the fields, but more men than women work in the fields in Italy and for longer periods. Sandwith's Egyptian eases show more men, and he thinks that it is beeause the women are not field laborers to the extent that they are in Italy. In Ameriea the women, as a rule, are not field laborers, and probably the vast majority of women pellagrins in this eountry never work in the fields. Some of them pick eotton in the fall for a very short time in the South, but this hardly aeeounts for the eause. In Italy and the southern states one may see large num-

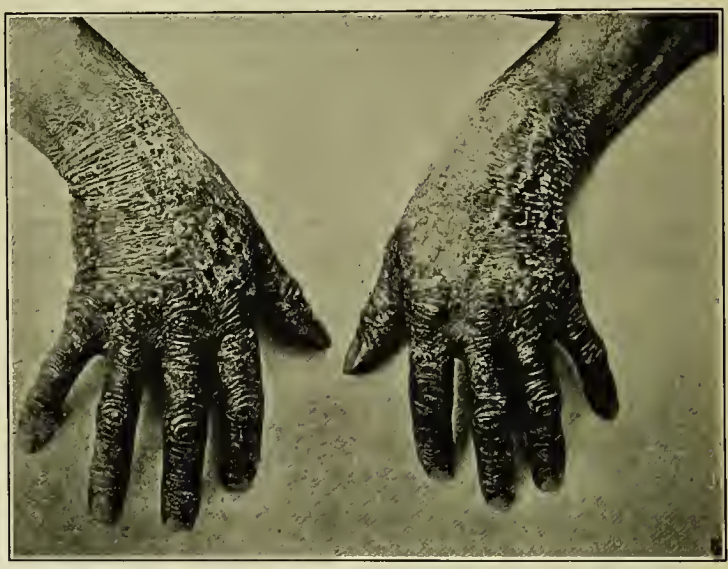


Fig. 2.—Dermatitis on hands of pellagrin. Skin dry, with exfoliation. Note the wrinkles. (After Merk.)

bers of women doing the washing for the family in some sheltered swamp cove where a spring arises or beside some running stream. This work takes the women outdoors far more in Ameriea than any farm work. Furthermore, men are far greater eonsumers of eorn produets than women. It is eertain that the prevalence of the disease among females ean not be attributed to the additional burden of childbearing. It is as natural for women to bear ehildren as for men to work, and, what is more important, the same preponderance of females holds in eomparing pellagrins of both sexes under 18 years. Women are neither more predisposed nor

less resistant to pellagra than men, and we must look to a greater exposure of women to the active cause of pellagra to account for the greater number of female pellagrins. This matter is discussed further in Etiology, page 263.

IS PELLAGRA INHERITED?

One of the questions asked of the physician, and one he often asks himself, is whether pellagra is inherited. Heredity is too vast a problem to be dismissed with a "yes" or "no" until one knows exactly in what way the word heredity is used. The understanding of the heredity of diseases is not as easy as counting chromosomes or comparing colors in the offspring of animals. There are as many opinions on the question as there are writers on the subject, and the answer has depended largely on the opinion of the writer.

Another unconscious influence has held sway—more, perhaps, than has been realized. This relates to the theory one accepts as to the cause of the disease. It is obvious that if one accepts the corn theory, and believes the disease due to toxins acting in the same individual for a number of years, it is very easy for him to believe that the same toxin can easily ensconce itself in some organic way in the ovum, reappear in the child, and continue to poison the infant. If one accepts the parasitic theory of the disease, he must either refuse to believe in its heredity or else postulate a new theory based on the idea that the cause is a germ or parasite with which the embryo becomes infected. One asks, if a toxin continues to act for ten years in the body or somatoplasm, why may it not continue to act through the germ plasm; the other refuses to believe the disease inheritable, or believes the embryo may become infected with the unknown organism.

Viewed from the accepted idea of modern medicine, a disease is inherited when the child has the disease at birth, as when a syphilitic child is born of syphilitic parents. It begs the question to say that syphilis is not inherited because the embryo was infected by the spirocheta pallida during gestation. One or both parents had syphilis, and their child at birth had the disease, illustrating the direct transmission of disease from parent to offspring. In the sense, then, that the germs or parasites may be contained either in the ovum or spermatozoon, or that the toxins may affect

these, or may through the fetal circulation and the placenta cause the disease to be present in the child at birth, one may say that pellagra is distinctly not inherited. As Sambon well says, there is no record of a child born with the characteristic signs of the disease upon it. Children are born with syphilis, but children are not born with pellagra. The disease pellagra in one or both parents does not reappear as the disease pellagra in the newborn infant. Even Lombroso, who believed firmly in the heredity of pellagra, did not believe the disease appeared in the offspring before the second year, and then not as pellagra, but as pellagra without the

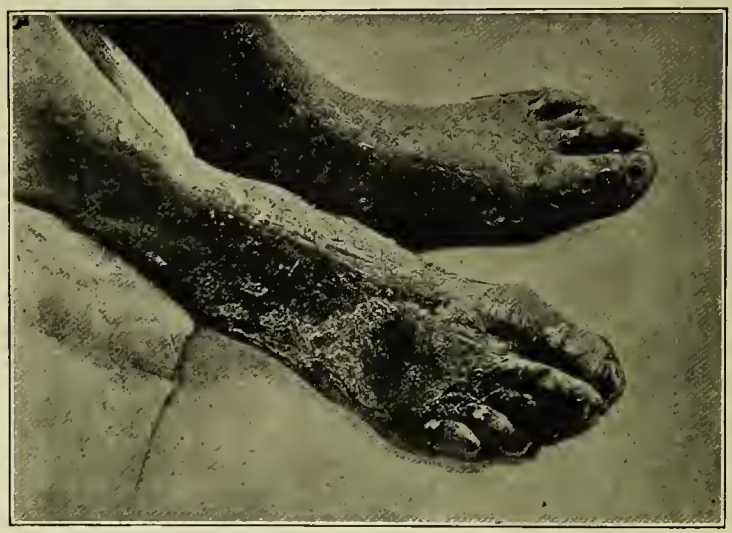


Fig. 3.—Dermatitis on feet of pellagrin. Skin peeling, with edema on left foot. (After Merk.)

eruption—pellagra sine pellagra—but we shall see that he mistook the degeneracy caused by pellagra for hereditary pellagra. At this point has originated the difference of opinion and the various beliefs regarding its heredity.

Pellagra is too recent in America to permit any statistics on heredity, but the family reported by Watson had three children, all pellagrins; both parents healthy, all living under the same conditions, and yet only the children developed the disease. Here healthy children developed pellagra, but, had they been born with a congenital weakness of any organ or feebleness of the entire system, it is reasonable to believe they would have developed pellagra

or any other disease very much more easily. A pellagrous parent is not a healthy ancestor, and predisposes his offspring to the attack of any widely prevalent disease.

Heredity depends on the quality of the sperm, the quality of the germ, and their suitability to each other. Gross errors in either parent tend to reappear in some form in the offspring, and particularly is this true of neurotic errors in the parent. An epileptic or a hard drinker is not apt to produce a child without some flagrant neurosis or mental weakness. The pellagrin suffers not only a chronic neurasthenia, an ever increasing tendency to melancholia, but also actual organic changes in the cord and brain. These organic changes do not appear in the child, but the stigmata of degeneracy do appear. Pellagra is not inherited, but the result of its ravages in the parent is inherited, and appear in the child in the form of dwarfism, deficient development, anemia, various malformations of the skull, asymmetry, bad set ears, mental weakness, slow growth, an unusual lack of resistance, and a frailness out of all proportion to age. In addition to pellagra, the parent may also have ankylostomiasis, or be tubercular, syphilitic, or alcoholic, and the degeneracy in the child would thus be increased. Let this continue for two or three generations, and it is natural to find the descendants of pellagrins suffering with the widely prevalent disease of the community, and increasingly degenerate and pauperized. Pellagra thus becomes a real cause of race degeneracy. These children live under the very same conditions in which their parents developed pellagra, and their very degeneracy is, in turn, an invitation to the disease already widely prevalent. If strong men develop pellagra, frail children will develop pellagra much more easily. The injurious influences are at work, and both parents and children may be attacked at the same time, or children may become pellagrous first and their parents afterward. The excellent table on page 38 prepared by Boudin is worthy of study.

The first three groups, with pellagrous parents, give 443 pellagrous children, while the last two groups, with parents well, give 297 pellagrous children, an excess in favor of pellagrous degeneracy and predisposition of only 20 percent. Even this is enough to furnish evidence that adult pellagrins should not marry and add a burden to the race in the form of degenerate children. Dr. Fritz, at Inzago, in the province of Milan, told me that he had noticed that pellagrous children, attacked in early childhood and

recovering rapidly, often married and had healthy families, with no pellagrous children. The disease in them did not pass the initial stage or become confirmed, and they were healthy men and women when they married.

Parents.	Number married couples.	Pellagrous children. Boys.	Girls.	Total children.
Father and mother.....	96	116	146	262
Father pellagrous, mother well	160	64	49	113
Mother pellagrous, father well	175	30	38	68
Father and mother well, two or more children pellagrous	43	59	53	112
Father and mother well, only one child pellagrous.....	185	80	105	185

1. Pellagra, as such, is not inherited.
2. The children of pellagrins are apt to be of inferior physique and have stigmata of psychophysical degeneracy.
3. Pellagra is thus a cause of race degeneracy.
4. Adult pellagrins should not marry.

AGE.

Pellagra may occur at any age. The youngest cases I have found were in infants of 4 and 5 months, and the oldest in a man of 99 and a woman of 102. Casal, Strambio, and Sambon report cases in octogenarians, and Siler found a case of 85 in Illinois, the oldest reported American case. In Egypt, Sandwith did not see any cases under 5, they were rare under 10, and most of the cases occurred in men in the prime of life. He considers puberty in boys a vulnerable time for the pellagrous attack. Sambon found in the country districts of Italy one family of eleven members, the youngest an infant of 16 months, all pellagrins; and a family of seven, the father aged 44, all pellagrins except the 4 months' old baby. Cases in children from 2½ to 10 years of age are found in the United States, but pellagra in infants is certainly not as common as in Italy, or, if so, it is either overlooked or not reported. It is probable that, as the disease is studied in greater detail in the country districts, more cases will be discovered in children. Often in the little ones the erythema is so slight and transient, the other

symptoms not at all severe, that the disease passes unsuspected and unnotieed. This is eertainly the ease in Italy, and, in addition, the pellagrosari do'not take the younger ehildren and infants.

The summary of different groups of statisties from different eountries at different times permits a safe eonelusion. Potarea eollected 17,027 eases of pellagra, and found 13 pereent under 20 years, 31 pereent between 20 and 40, and 56 pereent over 40. Strambio gives 129 eases, with 15 pereent under 25, 29 pereent between 25 and 35, 67 pereent between 36 and 60, and 3 pereent over 60 years. Calderini studied 352 eases in 1844, and found 83 of them under 3 years and 55 between 45 and 60. During the years 1905, 1906, and 1907 the pellagrosario at Rovereto, Austria, in the Tyrol, treated 456 eases, with an average age of 32½ years. Of these 456 eases 275 were males, with an average age of 34½ years, and 181 were females, with an average age of 29 years. I have eolleeted 159 eases in the United States, reported ehiefly from the eountry distriets of the southern states, and it is interesting to note that the average age of these eases is 32½ years, or the same as the 456 eases from Rovereto. This gives 615 eases from Ameriea and Italian Austria, with an average lower by 18½ years than the 130 eases from Illinios, with an average of 51 years, reported by Zeller. It is true that the average age of pellagrins in any state is lower than the average age of the insane pellagrins in the asylums of that same state; and, while most of the pellagrous area of the Union is not in the vital statistieal area, we may assume with reason that the average age of pellagrins is in the fourth deeade, and nearer 30 than 40. The Egyptian eases range around 40, while my own eases average 36 years.

1. Pellagra may oeeur at any age, the average being about 35 years.

2. By far the larger number of pellagrins are between 20 and 40.

3. Age influenees neither the severity of the attaek nor the eourse of the disease.

IMMUNITY.

The question of a natural immunity to pellagra is now merely a matter of observation, and ean not be deeided until experiment is substituted for observation, and then only after the eause of the disease is definitely known. Physieians and nurses are elearly

immune to the disease from transmission by contagion. The advocate of the corn theory believes all are immune as long as they do not eat corn, and the advocate of the parasitic theory believes in immunity as long as there is no infection with the parasite. The offspring of pellagrous parents is not immune, for he not only develops pellagra easily, but inherits a proclivity to disease in general. The inhabitants of an area where pellagra is endemic are not immune, because pellagra is there all the time, and individuals of their strength and environment constantly develop the disease. Furthermore, it is difficult to believe that a disease which admittedly is unable to confer acquired immunity is to any degree able to permit a natural immunity. Natural immunity is probably always only another name for variation in susceptibility. Individuals vary in susceptibility to pellagra as they vary in other diseases, and probably to a greater degree, as evidenced by the rapidly fatal and slowly chronic forms, the failure of certain individuals to develop the disease when living in the same environment, eating the same food, doing the same work, and exposed to the same influences as their brothers and sisters who become pellagrous. An individual may develop pellagra and be cured, or he may have pellagra with a recurrence ten years later. In this latter case there was either a reinfection or a reintoxication after a period of protection conferred by the first attack—a kind of pellagrous vaccination—or the parasites were latent this long period. A latent intoxication for twelve years is to me unthinkable. Parasitic infection permits and rather predisposes to reinfection, especially when the environment continues the same. There is probably neither a natural nor an acquired immunity to pellagra, but there is probably a variation in susceptibility to the disease, and certainly a variation in exposure to the causative agent. For instance, even when pellagra is epidemic, the crowded city escapes the disease, as illustrated by Milan, in Lombardy, in the last century. Even in country districts one area may be pellagrous, and another near by free from the disease, and this condition continue for long periods of time.

OCCUPATION.

At the Ospitale Maggiore, in Milan, pellagra is classified as a disease peculiar to farmers and peasants, just as lead poisoning is

confined to workers in lead. The triple cause of pellagra in the popular mind included this idea as expressed in the axiomatic phrase, "Peasant life, poverty, and polenta." That peasants, field workers, and farmers are peculiarly susceptible to pellagra is the opinion of writers in Spain, Italy, Egypt, and Roumania. Our experience so far in America does not agree with this altogether, and a study of Sambon's Italian report shows facts more nearly similar to conditions in America.

J. C. Johnson, of Atlanta, reports 20 cases of pellagra, with the following occupations: farmers, 2; merchants, 3; lawyers, 1; minister, 1; teacher, 1; salesman, 1; housewives, 10. From this series of 20 cases it will be seen that there are only two who worked in the fields, and that three of the four professions are represented. Consulting articles by different authors who report American cases, I find one group of 5 cases, all living in the country, but no farmers or field workers among them; another of 8 cases with only one farmer; of 6 cases one was a farmer and all lived in the country; of 10 cases 1 was a farmer, 1 a lawyer, 1 a carpenter, and the others housewives. It is probably true that a majority of the adult white pellagrins in America do not work in the fields, nor have I been able to find any record of pellagrous children who did farm work to any extent. What is of vastly more importance is the fact that practically all the pellagrins in America either live in the country districts, or in villages where the conditions and environments are the same as in the country. Procopiu says that pellagra exerts a preference for farmers, but it would be more correct to say that it exerts a preference for those who live in the country or in a rural environment, and this without reference to occupation. Environment, rather than occupation, is the predisposing and determining factor.

When I told Dr. Bezzola, of Milan, that pellagra occurred among the well-fed and highly nourished individuals in the South as well as among the poor, he expressed his astonishment and said that he even doubted that the disease was pellagra, so firmly was the idea of farmer and poverty as the united host of pellagra fixed in his mind. The physicians in the country districts of the southern states bear witness to the excess of female pellagrins and the rarity with which they work in the fields. Sambon found pellagra in coachmen, fishermen, priests, shepherds, carpenters, masons, in a shoemaker, and found in one case a hesitancy on the part of some

physicians to diagnose pellagra because the pellagrin was a cultured lawyer. He found in Italy, as is true in America, that members of the wealthiest families have the disease, but all these were rural in their habitations and lives. Of 1,955 deaths from pellagra in Lombardy from 1848 to 1859, the number of country people was 1,853; all the 150 lunatics in the asylum at Modena were from the country; of 148 insane pellagrins only 9 were not peasants, and even these were mostly born of pellagrous parents. About the same proportion holds in Corfu and in Roumania. Sandwith found of 137 cases 88 percent were peasants, 6 mason's laborers, 4 beggars, 3 boatmen, 2 policemen, 2 brickmakers, 1 potter, 1 servant.

I have seen three physicians in Georgia who stated that members of their families were pellagrous. They were cultured and refined men, and their families were in good circumstances. One mayor of a Georgia village developed the disease and died in a short time.

Pellagra is not limited to, nor does it exert a preference for, those engaged in any one occupation. Taking the pellagrous area of the world, it is probable that more farmers will have the disease than those of any other occupation—not because they are farmers, but because pellagra is limited to country districts, and a majority of the rural inhabitants are farmers. Probably a majority of American pellagrins do not work in the fields, but practically all American pellagrins live in a rural area.

CHAPTER II.

HISTORY AND GEOGRAPHICAL DISTRIBUTION.

In nearly every country in which pellagra has developed, the disease was known among the people in the rural districts before it was known in the medical literature of the country. The name pellagra itself was given the disease by the common people and not by a physician.

There are about sixty synonyms, which include names given by the people in Spain, Italy, France, Austria, Egypt, and America to the symptom complex known in medicine today as pellagra. Some of these are interesting in that they embody the double idea of symptom and of cause—as, for instance, scottatura de sol (the burning of the sun), which refers, of course, to the dermatitis and to the fact that the sun was at one time considered the cause of pellagra. Another idea conveyed by some of these synonyms is that pellagra at first was not considered as a separate disease, but a condition comparable to erysipelas, to scurvy, and to leprosy.

Among the synonyms that originated in Spain are:

Spanish Synonyms.

Mal de la rosa—sickness of the rose.

Mal de Asturias—the disease of the Asturias. This refers to the ancient province of Asturia in Spain, where the disease first originated. According to the redivision of Spain in 1833, this province took the name of Oviedo.

Mal del higado—disease of madness.

La gala de Saint Agnant, or sometimes written La gala de Saint Ignace—the itch of Saint Ignace.

Calor del hidago—burning of the person.

Escamadura del hidago—a desquamation of the person.

Flema salada—the salty phlegm. This refers to the salty taste occasionally persisting in pellagrins.

French Synonyms.

Mal du maitre—the master's disease.

Maladie de la Teste—the disease of Testa, Gironde, France. Pellagra originated in France in the vicinity of Teste.

Eruption de Lombardie—the Lombardian eruption. Pellagra originated in Italy in the province of Lombardia.

Mal de saintes mains—the sickness of the main saints.

Mal de Sainte Rose—sickness of Saint Rose.

Mauvais dartre—a bad eruption.

Italian Synonyms.

Mal della spienza—disease of melancholia.

Mal del monte—disease of the mountains.

Mal del padrone—the master's disease.

Mal del sole—the disease of the sun.

Scottatura de sole—the burning of the sun.

Jettatura di sole—the evil eye of the sun.

Umor salso—the salty humor.

Mal salso—the salty disease. These last two refer to the salty taste present in the mouth of some pellagrins.

Cattivo male—the wretched disease.

Mal della vipara—the disease of the viper.

Psychoneurosis maidica—the psychoneurosis caused by corn.

Pelandria, pellarela, and pellarina are dialectic corruptions of the ordinary pellagra. The first is used in the rural districts of Pavia.

Mal roxo, mal rosso—a blushing disease.

Pellis aegra—the rough skin.

Risipola Lombardia—Lombardian erysipelas.

Lepra Italica—Italian leprosy.

Maidica—the corn disease.

Malattia della miseria—the disease of the poor.

Raphania maistica—the corn shapping.

Malattia del insolata di primavera—disease of the sun's rays in the spring.

Calore del fegato—the heat of madness.

Salso—salty, biting.

Scorbuto mantano—mountain scurvy.

Scorbuto Alpino—Alpine scurvy.

Lepra Asturiensis—Asturian leprosy.

Elephantiasis Italica—Italian elephantiasis. Referring to the skin in the third stage.

Greek Synonym.

Græci elephantiasim—Grecian elephantiasis.

Roumanian Synonyms.

Buba tranjilor—refers to the pimples of the dermatitis on the back of the hand.

Rana tranjilor—refers to the roughness with the skin divided up with a supposed similarity to a frog's skin.

Parleala—a burning.

Jupuiala—a desquamation.

German Synonym.

Der Lombardische aussatz—Lombardian leprosy.

Egyptian Synonyms.

Inshuf—chapping.

Gofar—an eruption in camels and sometimes horses, and given by the fellaheen to the dermatitis in pellagra.

Among the synonyms which have become current in the English language are scorbutic paralysis, land scurvy, and Italic scurvy. An interesting fact is the origin of synonyms in the United States. Three are in common use among the people in the southern states, where pellagra is known as "the corn bread disease," "corn bread consumption," and "corn bread fever."

A study of these synonyms is very interesting, as it brings out some of the early ideas current concerning the disease. Mixed with these, of course, is an element of fact. Several of the synonyms refer to the sun, because in the early days the sun was believed to be the cause, and even now the part played by direct sunlight in the eruption is not clearly understood. Several refer to the mountains, making evident the fact, as is well known, that pellagra is found chiefly in a rolling country toward the foothills of the mountains as well as up in the mountains themselves, where the streams have cut deep and narrow valleys among the hills.

There are several references to the salty taste in pellagra and to the fact that pellagra is a disease of the poor. The word scurvy

as regards pellagra occurs because in the early days in Italy pellagra was considered a form of scurvy.

Different words relating to heat and burning are, of course, applied because of the sensations of burning often present in the hands and feet.

HISTORY AND GEOGRAPHICAL DISTRIBUTION.

The history of pellagra resolves itself into the history of the disease and its distribution in the several countries where it has appeared during the last two centuries. Pellagra may be said to have had six epochs, beginning probably about 1700 in Spain and extending to the present time in the United States of America. These six epochs may be called (1) the Spanish epoch, dealing with pellagra in Spain; (2) Italian epoch, dealing with pellagra in Italy; (3) French epoch, dealing with pellagra in France; (4) Austria-Hungarian epoch, dealing chiefly with pellagra in Austro-Hungary, Turkey, Roumania, and Greece; (5) Egyptian epoch, dealing with pellagra chiefly in Egypt and to a lesser extent in other parts of Africa; (6) American epoch, dealing with pellagra in North and South America, but chiefly in the United States. These epochs will be taken in order, and the history and distribution of the disease in each country discussed.

Spanish Epoch.

Pellagra originated in the northern part of Spain on either side of the Cantabrian range of mountains, which form that part of Spain known originally as the Asturias, but which is now on the northern side of the mountains the province of Oviedo and on the southern side the province of Leon. Casal wrote in 1735 in the city of Oviedo a treatise which he called the "Natural History of the Asturias," and in which what we know today as pellagra was called mal de la rosa—the sickness of the rose. His book was written in Latin, and it is interesting to know that this book has been translated into Spanish and printed in Spain in 1900. I found a copy of it in the British Museum. Thiery, a French physician, was familiar with the contents of Casal's treatise, and wrote a description of the mal de la rosa in the *Journal of Medicine* of France, 1755, II, 557. Casal's book was not really published until 1762.

Townsend, an Englishman, in his "Travels Through Spain" (vol. I, page 289, published in 1787), in writing of a visit which he made to the hospital at Oviedo, the capital of the Asturias, refers to this mal de la rosa, the first reference to the disease I have been able to find in the English language. Of this hospital he says: "The most remarkable cases were tertians, dropsies, and a disease peculiar to this province called mal de la rosa. This disease is considered a species of leprosy, and descends the sternum nearly to the cartilago xiphoides. Those who suffer with this disease have a peculiar propensity to drown themselves. When the disease is neglected, it terminates in scrofula, marasma, melancholy, and madness. The people among whom it originates eat little flesh in their food; they drink little wine. Their usual diet is Indian corn, with beans, peas, chestnuts, apples, pears, melons, cucumbers; and even their bread made of Indian corn has neither barm nor leaven, but it is unfermented and in a state of dough. Their drink is water."

From the province of Oviedo pellagra spread westward into northern Portugal and south into the provinces of Leon, lower Aragon, and Burgos. The second focus of pellagra in Spain seems to have been in the province of Guadalajara, just west of Madrid and in the midst of the Sierra de Guadarrama mountains. The third focus was in southern Spain in the province of Granada, in the midst of the many ranges of mountains in southern Spain.

The Academy of Medicine in Barcelona in 1879 made an investigation of the prevalence of pellagra in Spain, and, with certain limitations, according to Hirsch, the following facts may be accepted: The Asturias were the chief center of the disease at that time, and to a lesser degree lower Aragon and Burgos. In fifty villages in the province of Guadalajara 2 percent of the population were affected. The other provinces chiefly affected at that time were Cuenca, Navarra, Zaragoza, Zamora, and Galicia. A few cases were found in all the other provinces in Spain. Since that time the number of cases has decreased and the severity of the disease has greatly lessened. From a report of the Fourteenth International Medical Congress, held in Madrid in 1903, it appears that only twenty cases were observed in the Asturian districts where the disease first became known. There has been a marked decrease in the number of cases since 1900. Nearly all of the twenty cases above mentioned terminated by death of the infected person, largely

on account of lesions of the spinal cord. It is stated that the rapid decrease of the pellagra has been due to the general improvement in hygiene, food, and cleanliness among the laboring classes. For these facts concerning the present history of the disease I am indebted to Consul General Morgan, of Barcelona, Spain. There are probably more cases in the province of Madrid than in Oviedo at the present time.

Spain, topographically, is a rolling, mountainous country, consisting of hills, narrow mountain valleys, and swift-running streams. In those portions poorly watered a system of irrigation is used which dates from the Roman and Moorish periods. The chief cereals in order are wheat and barley, oats and rye. Corn is cultivated in all the provinces, but not to a great degree. Indian corn began to be used in Spain probably in the sixteenth century, and was doubtless brought there by the Spanish explorers from the West Indies and South America. The chief fact of importance in the history of pellagra in Spain is that it flourished for nearly two centuries, and then for some reason since 1900 has ceased to exist to any great degree.

Italian Epoch.

Pellagra next appeared in northern Italy. Sambon has investigated at great length the time of this appearance, and from the evidence presented it was certainly prevalent there in the year 1720. Dr. Bava said in 1781 that it has been known in the Ligurian mountains for over sixty years, and that it proceeded in the same order and manifested itself and grew with the same symptoms. Taraghi says the disease was noted before 1730 in the vicinity of Sesto Calende, on Lake Maggiore, just north of the present city of Milan. In these earlier days the oldest peasants said their ancestors spoke of it as mal rosso and mal della rosa, according to Alvera quoted by Sambon. Frapolli was the first to use the word pellagra, a name which originated among the peasants themselves. It is altogether probable, considering the later history of the disease and the fact that it has always seemed to have been present in a country a number of years before its discovery by the profession, that pellagra existed in northern Italy as early as 1700. The history of pellagra since its appearance in Italy has been largely its history in that country. Despite the fact that it first appeared in Spain, more cases have appeared in Italy than any-

where else in the world, and that country may rightfully be called the home of the disease.

Pellagra has existed in forty-four out of the sixty-nine provinces in Italy. Dividing Italy into northern, central, and southern portions, the disease first appeared in the compartments of Piedmont, Lombardy, and Venetia, which form northern Italy. It then spread gradually southward, but always tended more to the east than to the west, and has always seemed to avoid the Genoan littoral. In addition to the three compartments already mentioned, it has flourished in Liguria and Emilia; passing southward then into central Italy, it appeared in Tuscany, Marches, Umbria, and Latium, and to a small degree in Rome, Abruzzi, and Molise. It has avoided the southern compartments of Apulia, Campania, Basilicata, and Calabria. On the whole, however, pellagra has shown a constant tendency to extension southward. It has avoided the insular possession of Italy, and, strange to say, does not seem to have appeared in Corsica, Sardinia, and Sicily.

The following tables show in table No. 1 the deaths from pellagra from 1898 to 1905 inclusive; table No. 2, the number of pellagrins in the entire kingdom of Italy as taken by four different censuses; and table No. 3, the number of pellagrins enumerated in the chief regions of Italy according to the last three censuses.

TABLE NO. 1—MORTALITY.

Years.	Deaths from pellagra.
1898	3,987
1899	3,836
1900	3,788
1901	3,054
1902	2,376
1903	2,647
1904	2,363
1905	2,359

TABLE NO. 2—CENSUS OF PELLAGRINS.

First census (1879)	97,855
Second census (1881)	104,067
Third census (1899)	72,603
Fourth census (1905)	55,029

Notice the constant decrease since 1881.

TABLE No. 3—PELLAGRINS IN THE DIFFERENT NATIONS BY CENSUS.

Regions.	1881.	1889.	1905.
Piedmont	1,328	1,223	1,012
Liguria	56	30	56
Lombardy	36,630	19,557	15,746
Venetia	55,881	39,882	27,781
Emilia	7,891	4,617	3,357
Tuscany	924	1,125	1,137
Marches	406	920	1,426
Umbria	872	5,103	4,250
Latium	32	146	195
Abruzzi and Molise	.....	.....	.....

It will be noticed from these tables that the chief seats of pellagra have been Piedmont, Lombardy, Venetia, and Emilia. Pellagra seems to have originated in the district of Milan, then in Breseia, Bergamo, and Lodi, and then around Lake Como, Cremona, Mantua, and Pavia, so that by 1800 it covered praetieally all of Lombardy (Hirseh). In Venetia it appeared at Udine, far to the east of Milan and to the right of the Austrian Tyrol. In 1787 the naturalist and poet Goethe, in his Italian journey from Verona, speaks of seeing patients with pellagra. In Piedmont and Liguria it has never developed to any eonsiderable degree, and this is strangely true of Liguria. In Tuseany it appeared as early as 1785, but has not shown any marked increase in the last three eensuses. Hirseh as early as 1885 stated: "Pellagra in Tuseany in more recent years has established endemie eenters in the upper valley of the Arno, in Volterna around Lueea and Pisa, and among the hills near Florence. The disease appeared in Emilia about the same time that it appeared in Tuseany, though seven times more prevalent in the latter." In the last twenty-five years the disease has extended southward into the regions of Marches, Umbria, and Latium, and has been strikingly prevalent in Umbria. Now, aeeording to Hirsch, as pellagra has extended into southern Italy, the cases in the earlier seats of the disease have inereased—as, for instance, the history of pellagra in Lombardy shows that in 1839 there were 20,282 pellagrins; in 1856, 38,777; and in 1879 there were 40,838 out of a total urban and rural population of 3,653,941, or 11.2 pellagrins per one thousand. In 1889 the eases show a deerease to 19,557, and a further decrease in 1905 to 15,746.

The census of pellagra in Italy can not be relied on as more than approximately aecurate. The total evidenee, however, seems to show that at the present time there are about 50,000 pellagrins

in the kingdom. The number of deaths per year shows a continued decrease, so that there are probably less than 2,000 deaths per year from the disease, and that there are admitted into the asylums per year between 75 and 100 insane pellagrins. Certainly in Piedmont, Lombardy, and Venetia the disease is showing a rapid decrease, both in the number of cases and in the severity of the individual case. I found a good illustration of this fact at the Ospitale Maggiore in Milan. In former years several legacies were left to this hospital, the income from which was to be used in the treatment of pellagrins. The number of cases in the district of Milan and even in the adjacent country around the city had decreased to such an extent that there were practically no cases and no demand for help. It is probable that in the course of the next twenty-five years pellagra in northern Italy will cease to exist to any extent. This is in harmony with the history and almost complete extinction of the disease in Spain.

The Italian government, in view of the plague prevaleney of the disease, has taken various measures in an attempt to stamp it out. These measures have all been based on the idea that the cause of pellagra is in some way connected with Indian corn. Therefore in Italy corn is the official cause of the disease, and various measures and institutions for the relief and treatment of pellagrins have thus originated. One of the most famous of these was the law of 1902, and, while this law has certainly not been well enforced, there is a difference of opinion as to whether the decrease in the number of pellagrins has been due to what application this law has had or to other unknown causes. In Spain no preventive measures have been taken, and yet the disease has shown a greater decrease than in Italy.

Sambon quotes Professor Sanarelli, under secretary of state for agriculture, in regard to this law and its results as follows: "Notwithstanding the application of the law of July 21, 1902, for the prevention and eure of pellagra; notwithstanding the assiduous propagandism and the increasingly active endeavors of the provincial pellagra commissions; notwithstanding the great subsidies made by the state; notwithstanding the locande sanitarie, the exchange for bad maize, the dispensation of free salt, the encouragements given for the promotion of wheat eultivation, the teaching of sound agrarian principles, and many other direct or indirect measures excogitated by private initiative and by the government to effi-

ciently fight against pellagra, this disease in Italy does not show any tendency to decline in a satisfactory measure.

"It is true that in these last years the general death rate from pellagra has gradually diminished, and that at first sight this marked improvement might appear to be due to the application of the law of 1902. But in comparing either the number of pellagrins or the number of deaths from pellagra in the three years 1900–02—that is to say, before the application of the law—with those of the three following years, 1903–06, one finds that all these figures do certainly indicate a gradual, progressive improvement, but an improvement which takes place in more or less the same proportions. A legitimate doubt, therefore, arises as to whether it be right to ascribe the gradual decline of pellagra throughout the kingdom to the measures contained in the law of 1902."

The history of pellagra in Italy includes a reference to the measures used by the government to prevent the disease. Among these are the inspection of corn and the discovery and destruction of damaged grain. Some such measure as this was first authorized by the authorities in Venice in 1776. Efforts have been made to destroy damaged grain, but this law has been neither observed nor enforced. Practically all methods for the detection of damaged grain have failed. Sambon states that out of 44 Italian provinces affected by pellagra only 2, Venice and Padua, have a pellagrological inspector, whose duty it is to prevent the sale and consumption of damaged corn. Dr. Bresadola inspects corn at Rovereto, Austria. Efforts have been made to exchange sound corn for damaged corn, but this has been limited to one district in the province of Brescia. The royal law of 1884 tended to encourage the construction of plants for the drying of corn on the idea that corn spoiled and caused pellagra because it was gathered before it was dried. I have never been able to understand the necessity for these drying plants, because the Italian sun, like the Egyptian sun, is very warm, and what corn I had opportunity to examine in September and October was certainly dry and well seasoned. These drying apparatuses have never been used to any great extent. For a short time in Milan and Coma rural bake-houses were established which aimed to be model bakeries, cooperative in plan, and to cook good, cheap, wholesome wheat and corn bread. They were not patronized and were not useful to any degree.

Sporadic and spasmodic efforts have been made to abolish the

late varieties of corn on the idea that corn reaching maturity in the autumn in forty to sixty days was immature and unhealthy. In regard to this it may be said that the second crop of corn in Italy is certainly not as large or as well developed as the first crop, but whether this second crop has anything to do with pellagra is a matter of serious doubt. In the Austrian Tyrol there is no second crop of corn, and yet nowhere on the earth has the disease been fiercer in type. The law of Italy requires what is known as the notification of cases, or, as understood in America, the law requires the physician to report cases of pellagra when first diagnosed, just as the law in the states requires contagious diseases to be reported. For many reasons, economical and intellectual, this report of new cases is neither accurate nor honest. Sambon (Progress Report, page 37) discusses this matter in full.

Other measures include free meals to poor pellagrins for periods of not less than forty days twice every year. As Sambon wells states, this aims both to cure and prevent the disease, but the results do not seem to bear out the statistics. By thus giving away food the law is imposed upon, and often the poor and ignorant who are not pellagrous are fed. In other cases these locande sanitarie are so far from the homes of the pellagrins that they are unable to reach them. The pellagrosario is an institution established as a pellagra hospital. Only those who are pellagrous are admitted, and they are lodged, fed, and treated at an expense borne jointly by the local province and the national government. The first pellagrosario was established at Legnano, in the province of Milan, in 1784 by authority of Joseph II. of Austria. For some reason it was discontinued after four years, but during that time the elder Strambio was physician in charge and here made his fame. At the present time the pellagrosari at Inzago, Citta di Castello, Mogliano, Veneto, and at Rovereto in the Austrian Tyrol are the most important. At all these the inmates are decreasing from year to year, and, as Dr. Bresadola remarked to me at Rovereto, "soon the building will have to be used for other purposes, because there will be no more pellagrins." See page 65 for an illustration of the pellagrosario at Rovereto.

French Epoch.

Pellagra in France was first known through a report made by Hameau to the Society of Medicine in Bordeaux in 1828. He

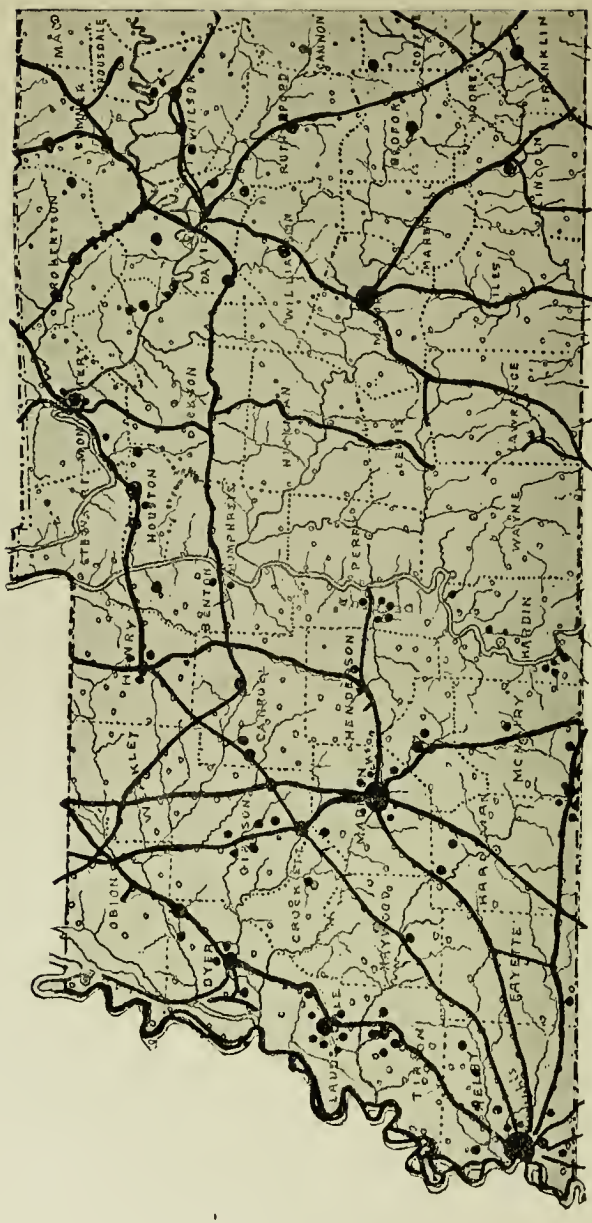


Fig. 4.—Map showing distribution of pellagra in the western half of the state of Tennessee. Pellagra foci are indicated by the heavy lack lines. (From Pellagra Report of the Tennessee State Board of Health.)

Fig. 4a.—Map showing distribution of pellagra in the eastern half of the state of Tennessee. Pellagra foci are indicated by the heavy black lines. (From Pellagra Report of the Tennessee State Board of Health.)

The maps of the two sections of the state of Tennessee show the relation of pellagra to principal streams, watersheds, highways of travel, and proximity of cases to each other. While most cases were found outside of corporate towns, some are charted as being in towns for the sake of clearness. The cases in the larger towns are for the most part from the surrounding country. Cases reported from counties not visited are not shown because their approximate locality is not known.

Fig. 5.—Map showing distribution of pellagra in the United States.

Note predominance in the southern states—sporadic elsewhere.

found the disease in La Teste de Buch, in the southwestern part of Gironde, a province of southwestern France bordering the Bay of Biscay. The disease was later found to have extended over the area known as the Landes, which lie to the south of Gironde. More cases developed in the latter than in the former department; further south, in the valleys and hills of the Basses Pyrenees, in the department of Hautes-Pyrenees, and further eastward toward the Mediterranean in the Pyrenees Orientales. North of the Pyrenees around Toulouse and in the department of Aude endemic centers developed. Later, cases drifted into Paris, and sporadic cases, according to Hirsch, were found in the department of Seine-Oise, Marne, Allier, Maine-Loire, Ille-et-Vilaine, and Rouen. Pellagra existed in the regions south of Bordeaux from the time it was first observed by Hameau in 1818 for about fifty years, but since 1890 it has practically been an extinct disease, though during the last quarter of the last century a few cases were admitted to the asylums for the insane. At the present time pellagra is not indicated in the French health statistics, and, if there are any isolated cases developing among the Pyrenees, they are either overlooked or not reported.

The region in southwest France, where pellagra formerly flourished, is among the hills and valleys at the foot of the Pyrenees mountains. It extends then northward along the coastal plain; it is a country intersected and cut in all directions by flowing streams. The Landes was formerly a very unhealthy country, and the novel "Maitre Pierre" was written to show the unhealthiness of this region before it was drained. A French proverb refers to the ravages of pellagra in this area:

"Taut que Lande sera Lande,
La Pellagra te demande."

"As long as the Landes are the Landes,
Pellagra will demand you."

The cause of the disease in this country was laid to many things, as air, water, food, millet seed, rye, maize, sardines, and salted eels. Corn is still cultivated in the Landes, the Basses Pyrenees, and adjacent departments in southwestern France. This area is just across the Pyrenees mountains from Spain and to the northeast of that country.

Austro-Hungarian Epoch.

The Austro-Hungarian epoch includes the distribution and history of pellagra in that area extending from the Austrian Tyrol on the west, Poland on the north, southward and eastward to Bessarabia, Turkey, and Greeee. The Austrian Tyrol lies to the north of and between Lombardy and Venetia, and the development of pellagra here is principally an extension in point of time from these two regions. In 1875 to 1905 eases were numerous and severe, but at present show a decrease in number and in severity. I saw some of these pellagrins at Rovereto, a town in the Tyrol, at the foot of the Alps. Pellagra crossed the Transylvania Alps, which separate Hungary on the west from Roumania on the east, and appeared in the latter country about 1830. The elder Theodori assigned its first appearance to the year 1833, and the first patient was admitted in the hospital in 1846. It has continued to spread and increase in Roumania, which is divided into the two compartments of Moldavia and Wallachia. Felix, according to Hirsch (1878), estimated that there were 4,500 pellagrins in Roumania, not quite 1 per thousand of the whole population. Since that time the disease has constantly increased, and it is estimated that out of a population of 5,000,000 there are probably 75,000 pellagrins. Berger in 1888 found in the district of Gradisca, where he lived, 790 pellagrins, 1.2 percent of the population. This district is in the western part of Austria, on the Italian frontier. It would seem that in the last twenty-five years the disease has constantly tended to decrease in the western part of Austria and to increase in the eastern part. It will be noted, too, that both of these areas are mountainous sections, the surface rolling in character, and in both sections corn is raised. According to Benjamin Triller (Thesis, Paris, 1906) the disease is also increasing in Servia and Bulgaria. Cases have been reported from Poland, southwestern Russia, Croatia, Dalmatia, Servia, Bosnia, and Herzegovina.

Consul General G. Bie Ravendel investigated for me the prevalence of the disease in Turkey, but found it so rare—comparatively unknown—that little definite information could be obtained. The disease is probably more prevalent in the rural sections of Turkey than has been known or reported. In Greece at the present time it is a rare disease, and is certainly not increasing. According to Consul General Gates, Athens, Greece, a case is occasionally re-

ported, but chiefly from Thessaly in the mountains of northern Greece. Contrasting these two countries, Turkey and Greece, in respect to corn, it is found that in a good year in Turkey the corn crop amounts to from 140,000 to 160,000 tons, and in a bad year from 30,000 to 40,000 tons. On the other hand, in Greece, according to Consul General Gates, the amount of corn raised is negligible, the principal crops being wheat and barley. The island of Corfu is off the western coast of Turkey, across the Adriatic from Italy. Information about pellagra in this island is furnished by Thypaldos. According to him the first appearance of the disease was in 1839, but it became rather endemic in character, and in 1867 it prevailed in twenty-seven out of one hundred and seventeen rural communes in the island, the cases representing about 3.2 percent per one thousand of the population.

Egyptian Epoch.

Pellagra was first discovered in Egypt by Prunner, and he described it in 1847 under the heading "Leproses" as follows:

"Pellagra is sporadic in Egypt, and such as we have studied it in Milan. We have seen three cases of it among the peasants, one of whom presents today, twelve years after our first seeing him, a brownish exanthem, paresis of the upper limbs, with retraction and muscular atrophy." Up to the time of Sandwith this is the only reference made to the disease, except one by Dr. A. Figari Bey, who writes of a venereal disease in lower Egypt with "a kind of leprous pellagra." F. M. Sandwith, while at work on a paper on hookworm disease in 1893, became aware that some of his patients among the peasants, to use his own words, "were suffering with dermatitis, bald tongue, diarrhea, pains in the back, alteration of the knee jerk, insomnia, and melancholia, all symptoms which could not legitimately be attributed to the anemia caused by the hookworm." It is, therefore, apparent that Prunner was right, even though so eminent an authority as Hirsch said that his description "does not by any means correspond to pellagra." The disease has, therefore, been in Egypt certainly for nearly seventy years and probably longer. It is far more extensive in Egypt, as outlined by the studies of Sandwith and Warnock, than has been supposed. The latter speaks of finding "scores" of pellagrous children.

According to Sandwith, pellagra in Egypt extends as far south as Assouan, or the tropic of cancer, latitude 24 degrees north. In 1897, 178 cases were admitted to the Cairo hospital and the home of 164 determined. Of these 37 came from upper Egypt and 127 from lower Egypt. Sandwith adds these two sentences: "The peasants in upper Egypt eat chiefly millet or sorghum vulgare, and not maize. The disease is said to be absent in Luxor, where no maize is eaten, but I saw several cases there." In 1891 Myles found it among the Arabs at Tokai on the Red Sea. In Egypt, as elsewhere, it is a country disease, and rare in such Egyptian cities as Port Said, Suez, and Alexandria. There is no polenta eaten in Egypt. Corn was brought from Syria into Egypt about 1840, and the peasants eat the variety called the camel's tooth, which is sown in July and ripe in November and December. According to Triller the disease has been found in Tripoli and in Tunis. Sandwith, during the South African war, found two cases among the lunatics at Robben Island, Cape Town, and he had previously recognized a third case in London which had been imported from South Africa. Physicians practicing in South Africa told Sandwith that they had never seen the disease in that section, but the two cases he found at Cape Town show that it exists there to a degree. Dr. W. M. Eaton, medical director of Rhodesia at Salisbury, Africa, states that "this disease has not been recognized in the territory."

The meager facts at hand regarding the distribution and existence of pellagra in Africa show that it is found at Cairo, in the parallel of latitude 30 degrees north, and at Cape Town, on the extreme of the African continent, latitude 34 degrees south. A further study and investigation in Africa would probably show a far wider distribution. I questioned very carefully in London the general agent of the African territory of Rhodesia, who is very familiar with the habits, customs, diseases, and foods of the people in that country, and, though I failed to gather from his very thorough description any evidence of the existence of the disease in Rhodesia, his opinion is borne out by Dr. Eaton quoted above. This is very interesting, too, in view of the fact that Rhodesia is an enormous corn-growing country. The samples shown me in London were the finest and largest ears, with the largest grains, I have ever seen.

Two cases of pellagra have been reported as originating in the British Isles, but there is some difference of opinion as to whether

the diagnosis was correct. At the meeting of the British Medical Association in 1898, Sandwith exhibited to physicians from India photographs of the Egyptian pellagrins, and three of these recognized the disease as existing in India. I have searched the records of the Indian medical congresses, but failed to find any reference to the disease. Dr. W. H. Jefferys, the coauthor of Jefferys and Maxwell's "Diseases of China," wrote me in response to an inquiry as to the existence of pellagra in China:

"My colleague, Dr. A. W. Tucker, suggested a long time ago that we should make a special point of looking out for pellagra in our Shanghai (China) clinic, and we did so and have never seen a case. Our clinic is a very large one, and represents Chinese from almost every province of the republic. Many of these patients are not, of course, of the farmer class, so they bear little on the subject.

"The Chinese eat practically no corn. I think this is a correct remark for all China. They grow a little for the use of foreigners in the treaty ports.

"I have been misled far too often, and become very conservative about predicting that a disease does not exist in China, and, therefore, I can not make such a statement. I can tell you, however, positively that pellagra has never been reported from China. Yet even that does not mean much, for I do not think that the average surgeon or physician would recognize pellagra unless on the lookout for it, or unless its great prevalence as a disease should force his attention."

I have not been able to find any records of the existence of pellagra in Australia. Dr. Hubert M. Hewlett, of Fitzroy, Victoria, Australia, has been on the lookout for the disease in that continent, but has so far failed to find any record of it or any case of the disease. My friend, Mr. D. P. Mitchell, a mining engineer of Australia and a gentleman of exceptional powers of observation, told me that the disease was unknown there.

American Epoch.

This epoch includes the history and distribution of the disease in the western hemisphere, and naturally falls into two divisions:

1. Pellagra in North America, including Mexico, Panama, and the West Indies.

2. Pellagra in South America.

1. North America.—Pellagra was first discovered and reported in America in 1864 by Dr. John T. Gray, of Utica, N. Y. A second case was reported verbally at the same time by Tyler, of Summerville, Mass. There have been speculations as to pellagra existing among the soldiers during the Civil War, but this is a matter of doubt. In 1883 Sherwell, of Brooklyn, reported a case in an Italian sailor, and in 1889 Bemis, of New Orleans, diagnosed a case of pellagra in that city. From all the evidence it is probable that the disease existed in the Carolinas and in Georgia in the early eighties, though the cases were not diagnosed as pellagra and the disease itself was unknown. Sherwell reported another case in New York in 1902. These cases thus far referred to seem to have been sporadic or imported cases, but it is probable that the number of cases of pellagra in the United States has been increasing since 1890, and that the disease has existed in the United States since 1880.

It is interesting to know that Sandwith, in Egypt, while studying hookworm disease, discovered pellagra in that country in 1893. At this time he suspected the existence of pellagra in America, thinking that it "might exist unrecognized in the South, and at one time I requested my friends to put me in communication with the poorest folk of the maize-eating district. I was referred to a settlement in eastern Virginia for pauper negroes, but on investigation I found that the inmates lived in stone houses on pork rations, and I came to the conclusion that the word poverty represented no condition in America which could compare with the misery of the impoverished peasants of Italy, Roumania, or Egypt."

Seven years later, while in South Africa, Sandwith saw two cases of pellagra and again suspected the disease in the United States. The real beginning of the history of pellagra in North America and the discovery of the present epidemic began just as the real discovery of pellagra in Egypt began—by the study of hookworm disease. H. F. Harris, of Atlanta, reported "A Case of Hookworm Disease Presenting the Symptoms of Pellagra." In 1907 George H. Searey reported an epidemic of pellagra at the Mt. Vernon, Alabama, asylum for negroes. This epidemic existed during the years of 1906 and 1907. Babcock and Watson diagnosed the disease at the state hospital for the insane at Columbia, S. C., and their report marks the beginning of widespread interest in the disease in North America. In 1908 they studied the disease

in Italy, and identified American and Italian pellagra as one and the same disease. Their reports aroused the attention of physicians throughout the country, and to them is due the arousal of the attention of the profession in the southern states.

Assistant Surgeon C. H. Lavinder, of the United Hospital and Marine Service, studied the malady, and later Captain J. F. Siler and Captain Henry J. Nichols, of the medical corps of the United States army. Under the auspices of the State Board of Health of South Carolina a conference on pellagra was held in October, 1908, and a national conference on pellagra was held in South Carolina at Columbia in 1909. Surgeon C. H. Lavinder, Dr. J. W. Babcock, J. J. Watson, Zeller of Illinois, and Bass of New Orleans have written many articles on the disease, which have been helpful to the physicians in this country. Pellagra in America has increased very rapidly, especially in the southern states and in the Mississippi valley, during 1908 to 1911, and it is probable that the spring of 1912 will show an influx of new cases. The type of the disease so far has been more severe, more acute, of shorter duration, and higher mortality than in Italy, Roumania, or Egypt. The percentage of males is less in proportion than in Italy. For example, in the state of Tennessee, out of 316 cases 214 were females and 102 males, and in three counties in southeastern Kentucky out of 140 cases 111 were females.

The map on pages 72 and 73 shows the distribution of pellagra in North America. Much of the area where pellagra is endemic is not in the official registration area, and many of the statistics are merely estimates. The United States Census Bureau for 1910 reports 368 deaths from the disease in the bureau's registration area, and of these 71.5 percent were females. This, however, does not nearly represent the number of deaths in that year in the United States from the disease, since most of these occur in the country districts and are not reported at all, either to country, state, or national authorities. The census gives 69 deaths as occurring in Atlanta, Ga., more than occurred in any other city in the United States. As a matter of fact, hardly any of these cases originated in the city of Atlanta, but most of them came from the smaller towns and adjacent rural districts, and should really be classified as imported cases so far as the statistics of the city of Atlanta are concerned.

The states of the Union, according to reports received in

Fig. 6.—Pellagrosario at Rovereto, Austria, with the Alps in the background. A government institution for the treatment of pellagra, and only pellagrins are admitted. Dr. Probitzer is the director of the institution. This place was visited by the author in October, 1911.

November, 1911, as to the prevalence of pellagra in them, are here given:

Pellagra in the States.

1. Maine .....1 case in the state hospital for the insane.
2. New Hampshire....No cases reported.
3. Vermont .....1910, 2 cases in Addison county; both fatal. No cases since.
4. Massachusetts .....1910, 3 cases. No report since.
5. Connecticut .....No cases.
6. Rhode Island.....1910, in insane hospital, 7 cases, with 4 deaths; 2 males and 2 females. All these insane.
7. New York.....1911, 2 cases, with deaths. These were imported cases.
8. New Jersey.....1910, 1 case; 1911, 1 case in Somerset county.
9. Delaware .....No cases reported.

10. Pennsylvania .....January, 1911, to November 1, 1911, 8 new cases.
11. Maryland .....To January 1, 1911, 11 cases; from January 1, 1911, to October 1, 1911, 8 cases. Of the 1911 cases, 7 died and 1 showed improvement; 6 were white and 2 were colored; 6 females and 2 males. The case that improved was a negro girl 5 years old.
12. Dist. Columbia.....1911, 2 cases; 1 death.
13. Virginia .....1910, 350 cases. During 1911 there were not as many, but no estimate.
14. West Virginia.....1 case.
15. North Carolina....1911, during the first eight months there were 69 white and 40 colored deaths reported to the State Board of Health from pellagra from a registration area with a population of 348,057. This area includes all towns of over 500 inhabitants. Estimating the mortality at 20 percent, we have a total number of cases in North Carolina of 545.
16. South Carolina....Estimated, 1,000 cases.
17. Georgia .....Estimated, 2,500 cases.
18. Alabama .....Disease increasing. Estimated, 2,000 cases.
19. Mississippi .....Disease increasing. Estimated, 2,000 cases.
20. Florida .....At the close of 1910, 99 cases reported. Estimated, 250 cases.
21. Louisiana .....In June, July, and August, 24 deaths were reported. Estimated, 500 cases.
22. Kentucky .....Estimated, 500 cases. Specially prevalent in the mountain counties in the southeastern part of the state. Assistant Surgeon R. M. Grimm found 140 cases in the three counties of Whitley, Knox, and Bell.
23. Tennessee .....Pellagra prevails in sixty-seven out of the ninety-six counties in the state; 316 cases in these counties. Out of the sixty-seven visited, number of cases in the state estimated, 500. (See Report of Pellagra Commission appointed by the Tennessee State Board of Health.)
24. Texas .....July, 1911, 33 deaths from pellagra, and 35 deaths in August. Estimated, 1,500 to 2,500 cases.
25. Arkansas .....Disease increasing. Conservative estimate, 1,000 cases.
26. Kansas .....First 10 months of 1911, 8 cases; 2 fatal. Disease increasing.
27. Missouri .....Estimated, 10 cases.
28. Oklahoma .....September 30, 1911, 19 cases and 13 deaths.
29. Nebraska .....No cases reported.
30. Ohio .....February, 1910, 1 case at Ironton, O.; May, 1911, 1 case at Cortland, O.

31. Illinois .....1909, 192 cases, all in hospitals for the insane; 1910, 78 cases in hospitals and 5 outside; 1911, 48 cases in hospitals and 9 outside. Report of special commission to be published in 1912.
32. Indiana .....1 case reported, with death. Insane hospitals have been carefully searched for the disease, but no cases found.
33. Iowa .....1910, 3 cases; 1911, 1 case.
34. Wisconsin .....No cases originating in the state; 1 case in spring of 1911 in Milwaukee and 2 deaths in September, 1911, but these 3 cases contracted the disease in the southern states and went north with the hope of obtaining relief.
35. Michigan .....No cases reported.
36. Minnesota .....No cases reported. The state institutions, especially the hospitals for the insane, have been carefully searched and no cases found.
37. North Dakota .....No cases reported.
38. South Dakota .....No cases reported. Probably present, but not identified.
39. Montana .....No cases reported.
40. Wyoming .....No cases reported.
41. Colorado .....Previous to July, 1911, no cases reported. In July, 1911, 5 cases reported, and in August, 1911, 4 cases.
42. New Mexico .....No cases reported.
43. Idaho .....No cases reported.
44. Arizona .....To November 1, 1911, 3 deaths reported in the territory; 8 cases unofficially reported in 1910. No new cases in 1911.
45. Utah .....No cases reported.
46. Nevada .....No cases reported.
47. Washington .....A sporadic disease, with 3 cases, reported. No cases in the asylums for the insane.
48. Oregon .....1 case reported, and this a patient coming from one of the coast counties in Washington. Case rapidly fatal.
49. California .....First case reported in 1909, only 4 cases reported all told, with 2 deaths in 1910. There are probably more cases in California.

From these figures, out of the forty-nine states, including the District of Columbia, pellagra has originated and prevailed in thirty-three. This count of thirty-three does not include a state like Oregon, for instance, where pellagra was imported, but did not originate within the state. It is apparent that the disease extends from Maine to California, and that there is a skip in that

tier of states beginning with Montana on the north, extending southward through Idaho, Wyoming, Utah, Colorado, Arizona, and New Mexico. The disease, however, reappears in the three Pacific coast states, but does not seem as yet to have originated in Oregon. It is interesting also to note the presence of the disease in Illinois and its extreme rarity in Indiana and Ohio. Again, Wisconsin, Minnesota, and the Dakotas are a nonpellagrous territory. The disease, therefore, may be classed as sporadic in the New England and middle Atlantic states, epidemic in the southern states, and sporadic again on the Pacific coast.

It is probable that there are 10,000 cases of pellagra in the United States at the present time. These statistics were furnished by the different State Boards of Health throughout the country.

I have collected by means of return postal cards more detail facts concerning the distribution of pellagra in the state of Georgia. Topographically, this state may be divided into three sections. The northern, hilly and mountainous; the middle third, hilly, rolling country; and the lower third, flat. Pellagra is least prevalent in the southern part of the state and the number of cases increase toward the north. There extends across the state from Columbus through Macon to Augusta on the eastern border a line which is presumed to divide the northern hilly portion of the state from the southern portion, which partakes more of the nature of a coastal plain, and by far the majority of these cases originate north of this fall line.

COUNTIES IN THE NORTHERN THIRD OF THE STATE.

County.	Cases.	Deaths.	Condition.
Polk	75	25	Disease increasing.
Gordon	20	3	Disease increasing.
Clark	200[1]	50[2]	Disease increasing.
Fannin	12	4	Disease increasing.
Stephens	10	2	Disease not increasing.
Habersham	50	45	Disease increasing.
White	8	3	Disease increasing.
Cobb	15	15[3]	Disease increasing.
Madison	12	6	Disease not increasing.
DeKalb	150	50	Disease increasing.

[1] Two hundred cases in three years.
[2] With possibly 50 deaths.
[3] Fifteen deaths in last three years.

MIDDLE THIRD OF STATE.

County.	Cases.	Deaths.	Condition.
Newton	5	6	Disease not increasing.
Muscogee	100	25	Disease increasing.
Henry	14	..	
Clayton	3	..	
Monroe	30	12	
Meriwether	10	..	
Taliaferro	..[4]	4[5]	
Greene	25	5	Disease increasing.
Heard	5	5	

SOUTHERN THIRD OF STATE.

County.	Cases.	Deaths.	Condition.
Colquitt	2	..	
Worth	6[6]	4[7]	Disease increasing.
Berrien	5	..	
Dodge	None	..	
Decatur	6[8]	..	
Pulaski	None	..	
Burke	None	..	
Randolph	10	3[9]	
Coffee	None	..	

2. Mexico.—The mortality statistics for the city of Mexico for the eleven years 1900 to 1910 give 1 death from pellagra, which occurred in the sixth district of the city in 1909. The physicians and hospitals for the city of Mexico have not had any cases. A death from pellagra occurred in the city of Monterey, Mexico, in 1910. This patient was a physician who formerly lived in the United States, but he probably developed the disease in Mexico. Dr. George McDonald, who formerly lived in Mexico in the section around Monterey, told me that since coming back to the states he remembers three cases in his practice in Mexico who were strangely diseased, but that he is convinced now that they were cases of pellagra. The disease has prevailed quite extensively in Yucatan, a province in the southern part of Mexico. Pellagra developed there

[4] No cases at present.
[5] Four deaths in last three years.
[6] Probably 20 cases in the county.
[7] Four deaths in 1910.
[8] Six cases in last few years.
[9] Three deaths in last three years.

Fig. 7.—Group of eight boys, all pellagrins. (Photograph by the author on the steps of the pellagrosario at Inzago, near Milan, Italy.)

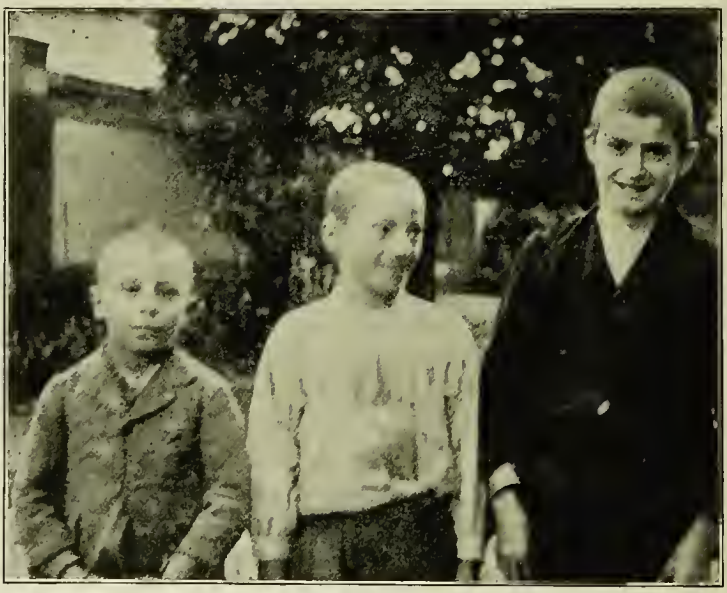


Fig. 8.—A closer view of three of the boys shown in Fig. 7.

between 1882 and 1891, and was very prevalent in 1907 and 1909. Gaumer is probably mistaken when he says that from 8 to 10 percent of the population are affected with the disease. Pellagra has, therefore, existed in the city of Mexico, Monterey, and Yucatan, and it is probable that an investigation of the disease in Mexico would show that it is more prevalent than is supposed, especially in the northern and central parts.

There is no positive evidence as to the existence of the disease in Central America, but Dr. John L. Phillips, under date of November, 1911, writes: "Pellagra was first diagnosed on the Isthmus of Panama in October, 1909. Since then we have had 32 cases, with 16 deaths." These statistics were collected by Dr. Phillips in the sanitary division of the Isthmian Canal Commission and are accurate. Pellagra probably prevails, therefore, throughout Central America in all that region north of Panama. The disease is also found in Jamaica, and occasional cases develop in Cuba, Porto Rico, and many cases occur in Barbados.

3. South America.—The existence of pellagra in South America is doubtful. Information regarding cases in Peru, Brazil, and Argentina is lacking, but one would not be surprised to find the disease more widespread in South America than evidence shows. I have searched the reports of the congresses on sanitation of the American republics, but I have failed to find any reference to or mention of pellagra. It is probable that the disease exists in Colombia, Venezuela, and Ecuador, though much positive information is needed for all this continent.

Fig. 9.—Map showing distribution of pellagra in the world.

Note relatively small pellagrous area,

CHAPTER III.

CLASSIFICATION.

Pellagra is a general disease, and in our nomenclature it should be classed as such. It is a systemic disease, and not a system disease; a disease of the whole organism, and not a disease of any one system of organs. It is not a skin disease, because it also affects and produces organic changes in the nervous and gastro-intestinal systems. It is not a disease of the nervous system, because it affects the cutaneous and digestive systems. It affects the nervous system as much as, if not more than, the digestive system, and therefore it can not be classified as a gastrointestinal disease. In Italy it is somehow preferably placed in dermatology, probably because the skin symptoms are so noticeable and have received so much attention.

Up to 1884 the Royal College of Physicians of London classified it as a skin disease, but since 1896 it has found a home among general diseases. It is no more a skin disease than syphilis or typhoid fever, though both of these have eruptions which help to confirm and to decide the diagnosis; it is no more a gastro-intestinal disease than yellow fever or tuberculosis, though both of these involve the abdominal organs; it is no more a nervous disease than sleeping sickness or leprosy, though both of these involve the nervous system seriously. Pellagra leaves its mark everywhere—on bone and parotid gland, cord and intestine, skin and stomach. It is a general disease, with a systemic pathology.

OTHER INFECTIONS IN PELLAGRA.

The tissues of a pellagrin offer fertile soil and little resistance to infection by bacteria, protozoa, and worms. Pellagra draws generously on the natural reserve force of all the organs, and it is natural to find several infections associated with the disease. The advance of tropical medicine has shown that the pellagrin is frequently a hospitable host to more than one parasite, and that the cachectic power of pellagra is aided by the blood extracting power

of several varieties of worms. Harris, studying ankylostomiasis, first discovered pellagra in Georgia, and Sandwith had the same experience in Egypt. The first record I can find of the presence of parasites in a pellagrin is in the elder Strambio's work on "De Pelagra." In case 9, at autopsy, he records "20 lumbrici in stomach and 7 in esophagus."

I have been surprised at the similarity in distribution of pellagra, uncinariasis, and malaria; and, since other intestinal parasites and protozoa are common in temperate and tropical climates along

Fig. 10.—Pellagrous boy. Very stupid, with vacant expression; body thin and gaunt. (Photograph by the author in Italy in 1911.)

with these diseases, pellagra is found associated with as many as three infections in the same patient. Pellagra by itself is serious enough, but pellagra associated with other infections endangers the patient far more. Pellagra diffused throughout the system, and hookworm inside removing constantly "the blood thereof which is the life thereof," causes darker clouds to rise on an already clouded prognosis. Amebic dysentery is found throughout the tropics and in parts of the temperate zone; in the United States it is the most common variety of all dysenteries. Pellagra involves the whole gastrointestinal tract, and, of course, would tend to increase an

infection with amebæ, and an amebic infection would tend to cause the pellagra to make greater inroads. Much attention has been given to amebic infection in pellagrins in the United States, but

Fig. 11.—Two Georgia cases, presented by the State Hookworm Commission. The smaller boy, aged 4 years, has had pellagra two years, and is also infected with hookworm; dry, wrinkled skin on hands, feet, and legs; marked diarrhea, rather constant; incontinence of urine and feces when picture was made; anxious, drawn, old-age expression of face; marked physical weakness and mental apathy. The larger boy, aged 7 years, has had same duration of symptoms, though less severe; skin eruption is slightly worse than that of the smaller boy; there are epithelial and blood cells in the feces, and the hookworm disease is present.

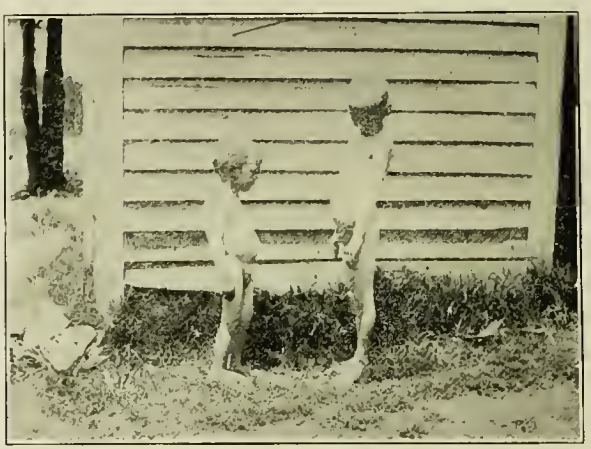


Fig. 12.—Same case as shown in Fig. 11. Side view, showing the protruding abdomen.

the prevalence of amebic dysentery in this country, plus the recurrent inflammation of the mucosa in pellagrins and the general lowered resistance, tends to explain the association of the two infections.

The following interesting table from Sandwith's Egyptian cases shows uncinariasis and bilharziosis in pellagrins during 1895, 1896, and 1897:

	Cured.	Relieved.	Not relieved.	Died.	Remaining.	Total
Pellagra and uncinariasis...	50	184	18	8	23	283
Pellagra, uncinariasis, and bilharziosis	19	99	3	9	24	154

This is a general death rate of 4.3 percent after deducting the cases still in the hospital, 6.9 percent for patients attacked by all three diseases, and only 3 percent for patients attacked by only two diseases. It seems that the additional infection by bilharziosis doubles the danger and the death rate. Of course the treatment of uncinariasis is far easier and more satisfactory of the two associated infections, and even a pellagrin shows marked improvement after the hookworms are gone.

Willetts, formerly pathologist to the Georgia State Sanitorium, examined the feces of 500 unselected insane negro females, and of these 35 were pellagrins; of the total number 250, or 50 percent, were infected with some form of intestinal parasite; of the 35 pellagrins, 14, or 20 percent, were so infected. Trichuris and ascaris predominated in the whole number, and strongyloides and uncinaria in the pellagrins.

Number examined.	Infections.	Ascaris.	Trichuriasis.	Strongyloides.	Uncinaria.	Hymenolepis.
500	250, or 50 percent	28.2	40.2	18.2	11.8	0.2
Number of these pellagrins.						
35	14, or 40 percent	8.57	17.14	25.71	20.0	2.86

Pellagrous children especially are apt to have hookworm and pinworm infections. The former may occur in pellagrins having only a mild attack, but hookworm disease is to be considered an enfeebling factor in pellagra, and some of the symptoms attributed to it—as anemia, emaciation, and weakness—may, in part at least, be due to the worms. This also applies to malaria, alcoholism, syphilis, tuberculosis, frequent pregnancies, surgical operations, or any condition of disease or stress that lowers resistance and invites prevalent disease of any kind. It is plainly true that with all the

members of a family equally exposed to the cause of pellagra, existing infections present in certain debilitated individuals act as predisposing factors to pellagra, and these individuals will develop the disease more easily than their strong and healthy relatives; and, vice versa, once pellagra is developed, other infections will more easily gain a foothold. Favus seems to have a preference for the scalps of Egyptian pellagrins. The physician often observes in poor children a paleness and lack of color and vivacity, due not to food nor to any disease, but to an absolute lack of food; it is the cachexia of indigence, and in endemic pellagrous districts predisposes to the disease.

Nichols' researches at the Peoria (Ill.) Asylum for the Insane enabled him to prepare the following very interesting table on protozoan infection in pellagrins, and to compare it with nonpellagrous inmates and soldiers in the Philippines.

	Pellagrous inmates.	Nonpellagrous inmates.	Soldiers in Philippines.
Number examined	88	101	454
Negative	14.7 percent	51.4 percent	48.8 percent
Amebæ	37	11	16
Flagellates (alone)	20	12	34
Encysted protozoa (alone) ..	27	24	..
Percent of cases with protozoa	85	48	51

The excess of protozoan infection in pellagrins is here very noticeable, being 37 percent greater than in the nonpellagrous inmates, and 34 percent greater than in the soldiers living in the tropical Philippines and subject to far greater changes in diet and variations in climate. Babcock and Lavinder found protozoan infections in pellagrins in South Carolina, and I have observed amebæ in a highly cultured woman with pellagra of several years' duration. The diarrhea in her case was persistent and more pronounced than any diarrhea I have seen. On autopsy of 18 of the pellagrins included in the above table, Siler and Nichols found ulcers in the colon in 12, or 66 percent, and 1 pellagrin "died of peritonitis following a perforation of an amebic ulcer;" 2 had tubercular ulceration and 1 trichinosis. In 1 case oxyuris eggs were found, but no uncinaria.

Siler and Sambon, working together in Italy, found ankylostoma duodenale, which is the European species of hookworm corresponding to the necator Americanus of Stiles, the most common

intestinal parasite in Italian pellagrins. Pisenti and Mandolesi state that those pellagrins who present the most severe anemic and oligemic symptoms "were those who presented the greatest number of hookworm eggs in their feces." Pellagra causes anemia, but the profound anemia in pellagrins necessitates the examination of the feces for hookworm ova. In the southern states it should be the first step in the treatment of pellagra.

Besides the hookworm, Sambon found ascaris lumbricoides, trichuris trichiura, oxyuris vermicularis, cercomonas hominis, ameba coli, and in one case the ova of hymenolepis nana. Strongyloides intestinalis is also found in Italy as well as necator Americanus. Summarizing the varieties of intestinal parasites found in pellagrins in Egypt, Italy, and America gives the following results:

	America.	Italy.	Egypt.
Ameba coli	+	+	+
Ankylostoma duodenale	—	+	+
Necator Americanus	+	—	—
Trichocephalus hominis	+	+	+
Oxyuris vermicularis	+	+	+
Cercomonas hominis	—	+	—
Hymenolepis	+	+	—
Schistosomum	—	—	+
Bilharziosis	—	—	+
Strongyloides	+	+	—
Flagellates	+	+	+
Trichina spiralis	+	—	—
Ascaris lumbricoides	+	+	—

The plus mark (+) indicates presence, and the minus mark (—) indicates absence. Some forms marked absent are probably present, but not reported. Intestinal parasites in pellagrins deserve a more detailed study, and its importance in treatment will become more apparent in view of the wide distribution of hookworm disease in the southern states. Either disease produces lassitude, weakness, dwarfism, anemia, emaciation, senile and wrinkled skin, dizziness, headache, gastralgia, stupid expression, and mental inertia. Pellagra is more susceptible of treatment after removal of hookworm infection. Both diseases are rural in origin, common among farmers, and with the same general geographical distribution; often to be found aggravating each other in the same individual, and their association may be expected in many cases.

RELATION OF PELLAGRA TO THE SEASONS.

Pellagra is a disease which avoids the winter. It usually first appears in the spring and early summer; it may reappear in the same patient in the autumn months of September or October, but usually it omits the autumn advent, hibernates during the winter, and recurs the following spring. In Italy the majority of the spring attacks occur between the middle of March and the middle of May, with extremes of invasion as early as February and as late as June. The autumn invasion recurs during September and October, with extremes of an early limit in August and a late limit in November. The latitude of 40° cuts the pellagrous area of Italy into northern and southern halves.

The pellagrous area of Egypt is cut by the latitude of 26° north, and therefore is about 1,000 miles south of the Italian area. The spring attack occurs from November to March; the majority of the cases make their advent and reach their acme during January and February. Few cases recur during the summer. The Egyptian climate is far more tropical than either the European or American, and January more nearly corresponds to spring in the latter two countries. In North America the pellagrous area is included between 25° and 45° north latitude, though by far the greatest number of pellagrins live in the belt on either side of the line 35° north latitude.

In Florida the spring invasion may occur as early as December and January, as in the case reported by Randolph; coming north into south Georgia, the spring attack may begin in February, and the farther north the later the seasonal attack. These represent the early appearances of the malady, but as a rule the greater number of cases in the southern states occur in April, May, and June. What is most surprising and apparently different from the usual cases described in the Italian and French literature is that the onset in America varies from January in Florida to late October, and one case is reported as recurring in November. I have seen cases whose onset included every month in the year except November, December, and January. One reason for this is the mild climate in the South, with only two or three months that could be counted severe, and even then the severity is not continuous.

Again, spring advances in this large country gradually, so that a 200-mile trip produces quite a change in climate and in the time

of advent of the seasons. As a rule, pellagra is synchronous with spring, recurring earlier in the year if the winter is mild and spring early, and later if the winter is severe and the spring late. Of 45 cases collected by Tucker of Virginia, 4 cases began in the summer, 4 in the spring, 2 no time given; of the 45 who gave the months, 2 began in January, 2 in February, 10 in March, 9 in April, 7 in May, 9 in June, 4 in August, 1 in October, and 1 in November.

It is important to remember that there are greater variations in the time of the first onset than in the time of the subsequent attacks. In America the first invasion of the disease may come in any month from late February to October, with an occasional case in January or November, but the recurrences are more periodic and uniform, and come with a vernal regularity. Case 3 in Chapter I (page 25) illustrates this uniform recrudescence in the spring. The autumn recurrences are practically limited to September and October, a more narrow limitation than obtains in the spring, and the autumn attack probably in a majority of cases fails to appear. One of the essential elements in the knowledge of the disease is the ability to diagnose pellagra in the fall or winter, when the disease conceals itself in the winter sleep. I have seen one case, about to recur in October, where the prodromes of epigastric uneasiness, slight diarrhea, vertigo, and weakness recurred, but no dermatitis, and in a few days the woman seemed strong and well. It is probable that if the disease in this case had taken deeper root and been more advanced, there would have been a typical autumnal recurrence.

INCUBATION PERIOD.

The period of incubation of a disease includes the time between the intake of the poison or the infecting agent and the actual onset of the disease. This incubation time consists of two stages: (1) the stage immediately after the infection or the intoxication, in which there are no external symptoms, as in the two to four days following the exposure of a child to scarlet fever; (2) the stage of prodromes, during which symptoms appear which are premonitory of the disease, as the appearance of sore throat before the actual onset of scarlet fever. The determination of the incubation period is not difficult when the cause of a disease is well known, because then the time of infection or exposure can be accurately ascertained. It is altogether different in pellagra, for the simple

reason that we do not know the cause, and therefore the incubation period is more or less a matter of *a priori* reasoning and speculation. Furthermore, the prodromal symptoms differ so widely in degree and in kind that even now the initial symptoms, not to mention the initial symptom, are still a matter of dispute. The prodromal symptoms vary from constipation to diarrhea, vertigo to dermatitis, and slight stomatitis to actual nausea.

It is evident that if an infant is born healthy, and develops pellagra during early infancy, the incubation period is slightly less than its age. Pellagra in a 5-months' infant previously healthy indicates an incubation period of less than five months. Furthermore, if a disease habitually makes its appearance in the early spring both in its first and subsequent attacks in the same individual, it is evident that the exposure to the intoxicating or infecting agent must be near the early springtime, or the intoxicating agent must be strangely and unaccountably cumulative at this time. Infants are peculiarly susceptible to intoxications, as indicated by milk poisoning, and to infections, as indicated by the various infective diseases common to childhood.

I have not been able to find in America pellagrous infants under one year, with one exception, but Sambon found infant pellagrins in Italy, and their ages reduce the previously estimated time of incubation. One infant was born in an Italian jail and nursed by its mother until 5 months old; it was then taken away and given to peasants living in the country. It developed pellagra in two weeks, or at 5½ months old. Another infant was born in November, and taken into the fields about the middle of March; it developed the pellagrous dermatitis in May. One of these developed the disease about April 1st and the other about May 15th. The incubation period in intoxications, such as meat and mushroom poisoning, ergotism, ice cream, and canned goods, is short, varying from twelve hours to a week, and usually near twelve hours—longer, of course, in ergotism. The time of incubation in infectious diseases is notably short, as in typhoid, cholera, malaria, smallpox, and influenza. Considered either from the history of the two infants given, or intoxications and infections in general, there is reason to believe the incubation period in pellagra varies from two weeks to two months, and probably nearer two weeks.

Another reason that complicates our knowledge of the disease is the insidious onset of pellagra. It insinuates itself into the system,

and even an intelligent pellagrin hardly knows from the prodromal symptoms how or when it started. Sandwith in Egypt, and Ludwig Merk studying in Austria and Italy, believe the incubation period to be from seven to nine months. Sandwith believes the poisoning due to corn from the previous year's crop, and the incubation probably as long as twelve months.

The corn crop is harvested in Egypt in November and December, and the majority of Egyptian pellagrins begin their eruption in January. He does not think sufficient fungi or poison could develop in this time to cause pellagra, and therefore makes the criminal out of the previous year's crop. This reasoning appears incorrect in view of corn as a cause.

Incubation is considered to end with the dermatitis, and, as fever is practically absent in the initial attack of pellagra, the erythema marks the close of the prodromal symptoms, and usually the definite onset of the disease. There may be no prodromal symptoms, and the dermatitis ushers in the attack.

DURATION OF PELLAGRA.

The duration of pellagra depends on the severity of the symptoms and the rate of progress of the disease. It is a chronic disease as a rule, but it occurs as an acute disease occasionally, and midway between these is a third form of moderate length. It is better to say that it is a disease of relatively long standing, whether the attack be acute or chronic. For instance, the acute form may last six weeks or three months, but this is unusually long for the average acute attack of a disease. Classified according to time, three types are found:

1. Acute Pellagra.—Malignant pellagra characterizes this attack. It lasts from one week to three months, and progresses rapidly to a conclusion. Fatal as a rule. It is also called typhoid, florid, tetanic, or fulminating pellagra.

2. Subchronic Pellagra.—Lasts not over two years and ends in death or recovery. Two subdivisions:

(a) Mild Subchronic Pellagra, or Convalescent Pellagra. There are one or two mild attacks, ending in recovery without subsequent recurrence. Pellagrous Italian boys, after one or two mild attacks, may develop into healthy men, and be accepted as soldiers in the Italian army.

(b) Severe Subchronic Pellagra, or Cachectic Pellagra. From the first attack there is rapid emaciation, the symptoms are pronounced, and cachexia comes quickly. There are no intermissions as in the chronic form, and death ensues in two years or less.

3. Chronic Pellagra.—This is the usual type in point of time, and it may last from three to thirty years, recurring regularly each spring or at longer intervals. It is mild and slowly progressive. It may end in apparent recovery, in insanity, or in death. Patients with this type are often not incapacitated from work, and may be apparently healthy during the seasonal intermissions of the disease.

Pellagra is too variable a disease to permit hard and fast lines of classification, and, as in nearly all diseases, different types grade insensibly into each other in actual practice. The chief features of the acute form are its rapid onset, high fever, and quickly fatal ending, but acute pellagra may terminate in either the severe subchronic pellagra or even the chronic form. The chronic form may occur for three successive years, disappear from external appearances, only to reappear in from three to six or ten years. In the same patient the disease may appear for several successive seasons, and then disappear for an equal time or longer.

There are problems that arise from this behavior of pellagra that are at present unsolved. Does reinfection or reintoxication account for the chronicity of pellagra? Is there a latent pellagra that explains its disappearance in a patient pellagrous for a number of years, or does reinfection account for the reappearance of the disease? Malaria is a disease which may appear as a result of long-standing latency, or as a result of reinfection. An individual moving from a malarial area to a more healthy center may for one or two springs have a malarial attack due to a latent infection, with subsequent improvement in health. He may return to the endemic malarial area and have a reinfection. Pellagra offers a stronger evidence of latency than malaria, for it is certainly latent from season to season, as it appears in the spring and disappears until the following spring, even if the patient is removed from the endemic area and no longer eats any of the products of maize. Since it is latent from season to season, it is reasonable to believe that it is latent for longer periods. Jansen, in 1788, saw the disease in Milan, and, referring to the end of the spring attack, writes: "The patients, however, are not now to be considered well; the

disease hides itself, but is not eradicated, for no sooner does the following spring return, then it quickly reappears.'' Strambio says pellagra, concealed after several successive seasonal attacks, ''is a snake in the grass.'' There is no reason for doubting the fact that reinfection recurs, and especially is this true if residence in an endemic center is continued.

Strambio, in 1787, found the length of the disease from onset to death in 10 pellagrins—7 men and 3 women—averaged five years and seven months, ranging from three months in the lowest to twenty years in the highest. Sambon found octogenarians in Italy who had ''donned the pellagrous bloom since childhood.'' I have found one North Carolina case with a clear history of duration of about twenty years, and, while the disease has been epidemic in the United States for an unknown period, probably not longer than twenty years, many physicians can make a baekward diagnosis of pellagra in former patients with a course of from fiftcen to five years. In Egypt the peasant pellagrin or fellah does not apply for treatment at the government hospital until he is too weak to earn bread, or until emaciation is present and cachexia is threatened. Of Sandwith's 162 hospital cases the average time they were ill before entry was two years; in 36 there was illness of less than one year, and 9 were ill for five years and longer. Siler investigated the number of previous attacks among pellagrins in Illinois, and found of 104 cases 25 percent had suffered three previous attacks, 52 percent two previous attacks, and 23 percent only one previous attack. My own cases in private practice average about three and one-half years. It is probable that the average length of the disease in Italy is between five and ten years, and in America and Egypt about five years.

DURATION OF A SINGLE ATTACK.

This ranges from the mild and often unnoticed attack in an infant, lasting a week, with an erythema hardly discernible, to the severe subchronic attack, which lasts from the initial onset to death, or from six months to two years. By an attack is included the premonitory symptoms, the dermatitis, with accompanying digestive disorders, and the gradual disappearance of the objective signs of the disease. The subsequent emaciation, weakness, and neurasthenic condition are to be considered the results of the attack, rather

than a part of it. A single typical spring attack, lasting from six weeks to three months, consists of three essential elements: (1) onset of the attack, (2) the outbreak of the attack, (3) the recession of the attack. A diagram will render the wisdom of division into these different periods clearly evident. The line *a b* does not coincide with the base line *A B*, indicating the lesions from the single attack.

1. Onset.—This period includes the prodromal symptoms, which begin toward the latter part of the period of incubation, and corresponds to the preërythematous stage noted by many writers. Its duration varies, but, as a rule, five to thirty days are the limits, with a probable average of fifteen days, or from two to three weeks.

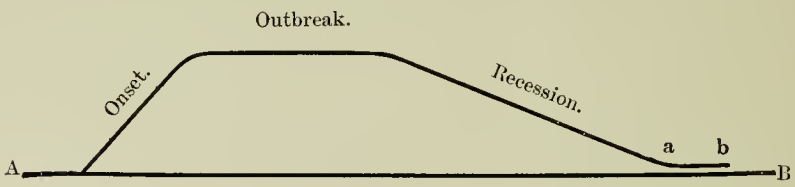


Fig. 13.—Diagram showing periods in an attack.

This period of onset may be altogether absent, and the dermatitis be the first symptom. Its severity is usually proportionate to the severity of the period of outbreak, and it, of course, closes with the advent of the outbreak. It is the period of minor symptoms, whose aggregate would lead both patient and doctor to use the word "bilious" or "spring fever." There is lassitude, general malaise, slight mental and physical inertia, lack of appetite, epigastric uneasiness, bulimia, coated tongue, occasional relaxation of the bowels, and a systemic desire to rest. At this stage the tongue, though coated, may present red, slightly swollen and occasionally cyanosed papillæ on the tip or edges, but no ulceration or buccal pain. It is a period of pathological introspection rather than of an objective disease. A burning sensation in the stomach, or on the hands or feet, is strikingly suspicious, and the occurrence of this group of symptoms in the spring in a patient in the country, especially if in an endemic pellagrous area, should make the physician both silent and careful.

2. Outbreak.—This period of outbreak closes the period of onset, and ushers in the objective symptoms that make pellagra so easy of diagnosis at this time of culmination of the single attack. The biliousness of the patient has become the pellagra of the physician.

The lassitude and malaise, the desire for rest and quiet, the mental and physical inertia, are now noises in the ears, vertigo, weakness in the lower extremities, occasional headache, increased reflexes, conversation is slow, the usual vivacity and force of the mind are

Fig. 14.—Pellagra during period of attack. Typical wrist band, raw tongue, and eruption on face. (By Dr. C. C. Bass.)

subdued and low, and depression has taken the place of the normal happiness of life. The backs of the hands are covered to a greater or less degree with a symmetrical dermatitis resembling a sunburn in the lighter attacks, and a sunburn with the tint of a full ripe

plum in the more severe attacks. Above the redness and around the borders the skin is rough; the elbows over the olecranon process are rough; there may be with this some roughness or dermatitis on parts of the face, neck, forehead, feet, and knees. There is an undue sensitiveness to sunlight or heat of any kind, slight pains in the abdomen occur, the pulse is faster, and fever is absent. The digestive symptoms of the onset are now really evident. The lips are red, the saliva is increased, and the tongue is smooth and of a beety nakedness; the papillæ are red and prominent, the tip and edges are raw in small areas; the soft palate, fauces, and throat are red and tender, and the esophagus seems in the same condition. There is actual diarrhea, with a peculiar odor to the stools, a sense of nausea develops, gas increases in the intestines, and one is reminded of an acute gastroenteritis. The facial expression is one of anxiety, the neurasthenic element arrives, and it is evident that some flesh has been lost. The patient is suddenly and temporarily a neurasthenic, with accompanying cutaneous and gastrointestinal symptoms.

3. Recession.—The period of outbreak continues from one week to a month, and, as the symptoms that characterize it begin to lessen, the period of recession has begun. The patient feels better, pains disappear, and appetite returns. The buccal and lingual areas return to their natural state, except the covering of the tongue seems strangely slow and delayed. The throat heals, and acid foods can be swallowed without burning. The stomach feels natural, digestion improves, the number of stools decreases and again assume their normal consistency. The dermotagrous area desquamates, and the skin becomes smooth. The erythematous area on the back of the hands desquamates in larger scales, and a cleaner, lighter skin, slightly pigmented perhaps, appears beneath. The ends of the fingers seem unusually pink and clean, and the sensations of burning depart. The face assumes its wonted brightness, and cheerfulness takes the place of depression and sadness. The step again becomes elastic, and the sense of well-being and strength returns. The pellagrin thinks he is well.

Pellagra, unlike a garment, is not made to pattern, and these symptoms are subject to great variation. These manifold symptoms vary in their order, in number, in association, and in severity. The first symptom may be the dermatitis, and for the first few seasons it may be the only noticeable symptom. There may be a

dermatitis and malaise, with entire absence of gastrointestinal symptoms. The skin may itch and burning sensation be absent. The attack may be so slight that it interferes with neither work, sleep, nor strength; or so severe that the first attack is malignant pellagra and death comes quickly. The dermatitis, instead of dry, may be of an exudative type, with vesicles, rupture, and ulceration. Constipation may occur and diarrhea be absent even in the period of outbreak. The neurasthenic element may be absent, weight may remain as usual, and good spirits instead of depression be the rule. Appetite may continue as usual, or even be increased to greediness. Thirst may increase, or there may be a repugnance to water. Lassitude, dermatitis, and the tongue without a coat are the rule.

ACUTE PELLAGRA.

The idea involved in the phrase "acute pellagra" is threefold: (1) it includes a pellagrous attack which is severe in its symptoms and prostrating in its effect; (2) temporary, limited, and not chronic in time; and (3) characterized by a fever, with extremes of 101° to 105°. These three ideas of severity, brevity, and fever caused the unfortunate term "typhoid pellagra" to be applied to this acute pellagra. Typhoid fever is one disease, and pellagra is another disease, and the two rarely occur together in the same individual. Procopiu and Watson each report two cases of typhoid in pellagrins, and even here it would be more correct to say that these pellagrins had typhoid fever complicating their pellagra, rather than to call the association of the two diseases typhoid pellagra. In this acute pellagra as it occurs the bacillus typhosus is not present, and the disuse of the term typhoid would be a gain in the nomenclature of pellagra.

The term "acute pellagra," as now applied to three conditions which occur, is (1) a primary acute attack of pellagra; (2) an acute attack in the course of the disease—sudden, severe, and febrile in its manifestation; (3) a terminal state of chronic pellagra, with prostration, convulsive seizures, fever, diarrhea, and emaciation. It seems hardly consistent to call the terminal stage of a most chronic malady the acute form of the disease, and a similar inconsistency arises when acute pellagra develops in the course of the chronic form. To be consistent, acute should apply only to

the primary attack, malignant in its nature. Pellagra is not noted for consistency, and acute pellagra includes all three conditions mentioned above. Each of the three is similar in symptoms and in duration, but each differs in the time in which it appears in the course of the disease. Classified according to time of appearance, they are as follows:

Acute pellagra.
Malignant pellagra.
1. Primary acute pellagra, first attack.
2. Secondary acute pellagra, developing suddenly in usual chronic form.
3. Terminal acute pellagra, ending cachectic stage, and fatal.

The duration of acute pellagra ranges from two weeks to three months; a duration of less than two weeks is extremely rare. It is sudden in onset, and the patient goes to bed at once. Prostration seems out of proportion to the fever, and the pulse is high in proportion to the fever, wherein it differs notably from typhoid fever. Rarely is the pulse lower than 120, often it runs to 130, and higher as death approaches. The heart is not enlarged, and the sounds seem humdrum and low; the fever is continuous, without any regular morning and evening variations. The pulse is small, often irregular. Procopiu calls it a filiform pulse. The coat of the red tongue is gone, and fissures cover the dorsal surface, a true dissecting glossitis. Stomatitis, pharyngitis, gastroenteritis, and rectitis are usually present. A serous diarrhea, stubborn and persistent, is more frequent in the terminal acute type, with an accompanying emaciation, which ends cachexia and ushers in marasmus.

Added to the difficulty in swallowing is dyspepsia, nausea, aversion to food and often to drink; prostration, loss of vital and muscular power, a fetid perspiration, and a peculiar pellagrous odor increase the general despair. The skin takes on a deeper hue, approaching lividity, and there may be the typical dermatitis and rough skin. Petechiæ may develop in the skin, bedsores on the supporting areas, trophic changes in the nails, wrinkled forehead, and rapid mummification. Instead of immobility and permanent dorsal decubitus, tetanic and meningeal symptoms arise, which are probably due to an advance of the pellagrous process in the cord and brain, with inflammation and exudate in some cases on the meninges and the cortex. Tremors, tetanic tossing to and fro,

convulsions, opisthotonos, emprosthotonos, localized muscular contractions, delirium, mutterings, mania, depressive states, and hallucinosis mark the departure of the intellect.

Toward the last, incontinence of urine and feces may develop. The urine is probably increased, excepting the rare cases with uremic symptoms. The specific gravity is low; hyalin and granular casts, with occasional corpuscular elements, and albumen are often present. The course of the attack is rapid, death the rule, and temporary recovery the exception. Such a patient never recovers from pellagra, but recovery from the attack may grant a temporary respite. Terminal acute pellagra is always fatal.

Differential diagnosis and post-morten findings will be found in appropriate sections. (See page 208.)

SUBCHRONIC PELLAGRA.

Convalescent Pellagra.

This is the least serious of the forms of pellagra. In itself it is proof that a pellagrin may recover permanently from the disease and that treatment is really worth while. Fritz, at Inzago, called my attention to this type of the malady and to its evanescent tendency. In his thirty years' experience he had often observed children who developed pellagra to the extent of a mild dermatosis and dyspepsia, and after not more than two years of pellagrous symptoms, usually one year, recovered, grew into healthy men and women, and never afterward had any pellagrous symptoms whatsoever. One of his patients, a boy, gained forty pounds in three months. This is true in Italy and in Roumania, and as the disease advances in America, and its different degrees of severity become more apparent, evidence will accumulate as to the convalescent form. Fritz' cases among the men married and raised large families, and that with no pellagra among their children or any stigmata of pellagra. The women married and bore children, often large families, and with no miscarriages. The boys, on reaching manhood, stood the rigid physical examination, were often accepted as soldiers in the Italian army, and became strong men and good soldiers. Under this division come also many of the cases that Sandwith found when he examined 352 presumably healthy men and boys in eleven different villages in Egypt, and found 127 of them suffering with unmistakable signs of pellagra.

Pellagra may be so mild that the pellagrin suffers no inconvenience and is unaware of the presence of any disease whatsoever. Infants and young children develop the disease and present to the mother no signs of sickness, play and run as usual, and eat and sleep as well as ever. Pellagra varies as much in its severity as in its mass of symptoms, and one to see convalescent types of pellagra has only to visit the various pellagrosari in Italy. In America this subchronic type is extremely rare as compared with Italy, but, as time goes on, the extreme virulence of American pellagra will probably decrease with an increase in the number of cases of the convalescent type.

Convalescent pellagra does not advance beyond the stage of initiation. It is the pellagra of dyspepsia and dermatosis, with the practical absence of all the neurasthenic symptoms. It is well known that the initial stage may last in chronic pellagra for ten years, but in the present form even the initial stage is not far advanced. The cause of pellagra fails to gain a foothold, its tendrils do not take root in the body soil, and after one or two vernal attempts it surrenders. Weight is the great mass symptom of pellagra, and here there is no emaciation and often no loss in weight. The metabolic processes proceed as usual, appetite continues, sleep is good, and work is not interfered with. Young people are most often affected with this type, and their natural reserve force and resisting power help to ward off the disease. Youth is the best medicine in pellagra.

The dermatitis is mild, rarely extends far above the wrist, comes quickly and goes quickly, leaving no objective change in the skin. The wet form never occurs in this type. The dermotagra is nearly always limited to the flexor surface of the forearm and to the elbow. The forehead may occasionally show a little branny roughness, but no dermatitis. The buccal mucosa is not very tender, though it is nearly always slightly red. The tongue does not have the entire nakedness, ulceration, and fissured glossitis of the more severe forms. It does not pain the patient to swallow, and digestion is rarely interfered with to any extent. For a day or two, rarely longer than a week to any extent, does diarrhea exist. The bowels are rather relaxed than loose, and constipation is often present; in many of this type no change occurs in the action of the alimentary canal of which the patient is aware. In two weeks to a month all signs of the disease are gone, and the health is as

good as ever. There may be one or two recurrences, but of no greater moment than the first attack. Anemia is not pronounced, weakness is not felt, and recovery is without incident.

Cachectic Form.

Strambio must have had this type in mind when he spoke of continuous pellagra. It is true that cachectic pellagra does have periods of remission, but they are so slight that both physician and patient feel that the disease is still actively present. There is really no level in cachectic pellagra, and down-grade is the rule. There is no up-grade, because the patient does not get better. The first attack is inordinately severe, even fever of 100° or less may be present, the pulse quickly rises to 100° and over, and the digestive symptoms are pronounced. The lips are red, often cracked and painful, and in one case I saw there was a continuous herpes on the lips. The tongue is red, with small ulcers on the tip and margins, and papillæ are prominent, and the circumvallate papillæ begin rising almost to the dignity of warts in their size and firmness. The soft palate, fauces, pharynx, and buccal mucosa are red, inflamed, and on the anterior pillars is occasionally a livid, cyanotic area which seems on the eve of ulceration. Indigestion, nausea, actual vomiting, diarrhea that is continuous, though not as severe as in the acute types, abdominal distention, gastralgia, and epigastric weights are so many separate blows on the general nutrition, and gradual loss of weight and emaciation introduce cachexia. After the first attack the patient is thin, cachectic, a profound neurasthenic, discouraged, mental activity gone, and despair and tears are moods in his neurasthenia.

The essential difference in this form is the absence of any real period of intermission. The attack continues, and the loss of weight gradually increases. The dermatitis may disappear, leaving a pigmented area in its trail. On careful examination the dermotagra remains on the elbows, flexor surface of the forearm, and even on the arms and shoulders, especially if in the primary attack the skin involvement had this area. The mouth rarely entirely heals, and, even if it appears well, in another week a new wave of inflammation sweeps over the mucosa of the oral cavity. The tongue never resumes its normal coat and state; on its tip and margins are red areas, and the papillæ are more or less prominent. Frequently the gums are red and tender, and toward the latter stages

receede, with a collection of putrefactive material on the gum edges, giving the appearance of the mouth in Riggs' disease. As a rule, the abdomen is flat, and in one case of a woman of 34 a typical boat-shaped abdomen was present even in the periods of active diarrhea. There may be burning in the feet, occasional nights of insomnia, and the temperature may rise to 101°, with five to ten stools daily for a week, and dissolution appear near. The fever and diarrhea abate, and the former ability to sit up and even walk may return. After one of the severe weeks the cachexia and general debility are more apparent, listlessness increases, the emotions come more to the surface, recurring attacks of erythema may develop, and the approach of death nears usually without pronounced symptoms of insanity. Sunken eyes, wasted face, keenly drawn fingers, and skin and bones represent what six to twenty-four months ago was a healthy, vigorous man or woman. I saw one case of this course in a girl of 8 years. At different times fever is present in this type, but not of the severity or length of the acute type. In women there is amenorrhea as a rule.

It should be remembered that in a spring attack, with a cachexia resulting in midsummer, the recurrence in September or October of an autumn attack may close the scene, though occasionally the patient may last through the winter until the following spring or summer. Even in midwinter the evidences of the disease are still present on the tongue, hands, and gums, with weakness, emaciation, and neurasthenic cachexia. This rapid course of the disease is more common at the present time in America than in Italy, though I am convinced from a study of the literature that this cachectic type was also common in Italy about the close of the eighteenth century. This type is chronic pellagra, with the omission of the stages of dyspepsia and neurasthenia, and with the early onset and rapid course of the stage of cachexia.

CHRONIC PELLAGRA.

Before one can understand pellagra he must have a general conception of the disease from its inception to its termination. It is a chronic disease, and, as time passes, the malady tends to progress. It is one thing to know pellagra at the acme of the spring attack, but it is another matter to comprehend the disease with its remissions and intermissions, its conglomeration of variations in season

and out of season, and the fact that, once firmly fixed in the system, the periodic attacks are vernal links in the chain of a steady progression toward cachexia, insanity, and death. Jansen, of Leyden, in his monograph on pellagra written in 1787, accents this idea in his definition: "An endemic disease usually manifesting itself first in the spring by rose-colored spots on the back of the hands, disappearing in winter, but which almost always recurs the following year full of more serious symptoms; at length attended by melancholia, mania, and convulsions; with exceptions here and there, it causes death."

Jansen wrote his work in Latin, and his description of the disease, splendid as it is, was improved by the excellent translation made by Chevalier, which appeared in the *London Medical Review and Magazine* in May, 1799. Chevalier's comments and translation constitute the first article in the English language on pellagra. This article takes into account the progressive element in chronic pellagra, and from it as a basis the different stages of the chronic form become apparent. I give Jansen's delineation of the clinical course in full, for I have found nowhere else in the literature so classic a description.

About the month of March or April, when the season invites the farmers to cultivate their fields, it often happens that a shining red spot suddenly arises on the back of the hand, resembling the common erysipelas, but without much itching or pain, or indeed any other particular inconvenience. Both men and women, boys and girls, are equally subject to it. Sometimes this spot affects both hands, without appearing on any other part of the body; not uncommonly it arises also on the shins, sometimes on the neck, and now and then, though very rarely, on the face. It is also sometimes seen on the breasts of women where they are not covered by the clothes, but such parts of the body as are not exposed to the air are seldom affected, nor has it ever been observed to attack the palm of the hand or the sole of the foot.

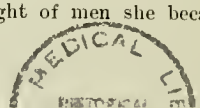
This red spot elevates the skin a little, producing numerous small tubercles of different colors; the skin becomes dry and cracks, and the epidermis sometimes assumes a fibrous appearance. At length it falls off in white furfuraceous scales, but the shining redness underneath still continues, and in some instances remains through the following winter. In the meantime, excepting this mere local affection, the health is not the least impaired; the patient performs all his rural labors as before, enjoys a good appetite, eats heartily, and digests well. The bowels are generally relaxed at the very commencement of the disease, and continue so throughout its whole course. All the other excretions are as usual, and in females the menses return at their accustomed periods and in the proper quantity.

But what is most surprising is that in the month of September, when the

heat of summer is over—in some cases sooner, in others later—the disorder generally altogether disappears, and the skin resumes its natural, healthy appearance. This change has been known to take place as early as the latter end of May or June when it has been only in its earliest stage. The patients, however, are not now to be considered as well; the disease hides itself, but is not eradicated. For no sooner does the following spring return, but it quickly reappears and generally is accompanied with severer symptoms. The spot grows larger, the skin becomes more unequal and hard, with deeper cracks. The patient now begins to feel uneasiness in the head, becomes fearful, dull, less capable of labor, and much wearied with his usual exertions. He is exceedingly affected by the change in the atmosphere, and impatient both of cold and heat. Nevertheless, he generally gets through his ordinary labor, with less vigor and cheerfulness indeed than formerly, but still without being obliged to take his bed; and he has no fever, his appetite continues good, and the chylopoietic viscera perform their proper functions. When the pellagra has arrived even at this stage, the returning winter nevertheless commonly restores the patient to apparent health; but the more severe the symptoms have been, and the deeper root the disease has taken, the more certainly does the return of spring reproduce it, with additional violence. Sometimes the disease in the skin disappears, but the other symptoms remain notwithstanding.

The powers of both the mind and body now become daily more enfeebled; feverishness, watchings, vertigo, and at length complete melancholy supervene. Nor is there a more distressing melancholy anywhere to be seen than takes place in this disease. On entering the hospital at Legnano I was astonished at the mournful spectacle I beheld, especially in the women's ward. There they all sat, indolent, languid, and with downcast looks, their eyes expressing distress, weeping without cause, and scarcely returning an answer when spoken to; so that a person would suppose himself to be among fools and mad people, and indeed with very good reason, for gradually this melancholy increases and at length ends in real mania. Many, as I had opportunity of observing in this hospital, were covered with a peculiar and characteristic sweat, having a very offensive smell, which I know not how better to express than by comparing it to the smell of moldy bread. A person accustomed to see the disease would at once recognize it by this single symptom. Many complained of a burning pain at night in the soles of their feet, which often deprived them of sleep. Some are affected with double vision, others with dementia, others with visceral obstructions, others with additional symptoms. Nevertheless, fever still keeps off, the appetite is unimpaired, and the secretions are regularly carried on.

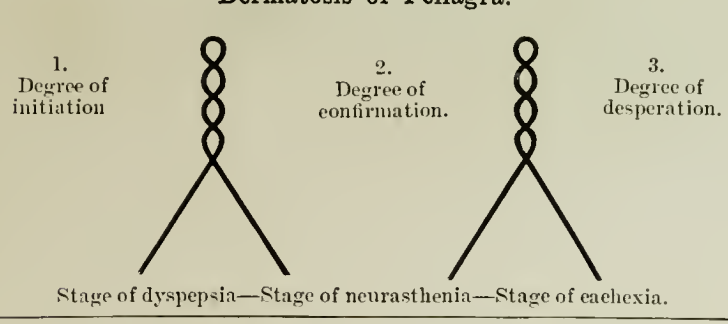
But the disease goes on increasing, the nerves are more debilitated, the legs and thighs lose the power of motion, stupor or delirium comes on, and the melancholy terminates in confirmed mania. In the hospital at Legnano I saw both men and women in this maniacal state. Some lay quiet, others were raving and obliged to be tied down to the bed to prevent them from doing mischief to themselves or others. In almost all these the pulse was small, slow, and without any character of fever. One woman appeared to have a slight degree of furor uterinus, for at the sight of men she became



merry, smiled, offered kisses, and by her gestures desired them to come toward her. Some were occupied in constant prayers, some pleased themselves with laughter, and others with other things. But it was remarkable, as Moscati observed, that all who were in this stage of the disease had a strong propensity to drown themselves. They now begin to grow emaciated, and the delirium is often followed by a species of tabes. A colliquative diarrhea comes on, which no remedy can stop, as has also been observed in nostalgia. Sometimes in pellagra the diarrhea comes on before the delirium, and the delirium and stupor mutually interchange with each other. The appetite often suddenly fails, so that the sick will sometimes go for nearly a week without tasting food. Not uncommonly it returns as suddenly, so that they eagerly devour whatever is offered them, and this even at times when they are horribly convulsed. The convulsions with which they are attacked are most shocking to see, and are of almost every kind; catalepsy is frequent, which has been described by writers. I saw one girl in bed who was violently distorted by opisthotonos every time she attempted to rise; some are seized with emprosthotonos, and others with other species of tetanus. At length syncope and death close the tragedy, often without any symptom of fever occurring throughout the whole course of the disease.

STAGES OF CHRONIC PELLAGRA.

The course of chronic pellagra can best be represented and understood by a diagram, with the dermatosis as the common basis, since it is common to all three stages and is the one objective symptom that connects the varying pictures of dyspepsia, neurasthenia, and cachexia.



THE DERMATOSIS OF PELLAGRA.
(a) Dermatitis or erythema; (b) dermotagra or rough skin.

Fig. 15.—Diagram showing stages of chronic pellagra with relation to clinical symptoms.

The time of a single pellagrous attack was divided into period of onset, outbreak, and recession, while the course of chronic pella-

gra includes a far greater length of time divided into relatively long stages. Periods in the single attack are to be distinguished from stages in the chronic course; the period refers to a short time and the stage to long duration, involving the idea of continuance. To a certain extent these stages are as abitrary in their separation and limitation as are the three periods in the recurrent single attack. Each stage in chronic pellagra consists of recurrent attacks of activity and times of intermission, or inactivity of the pellagrous advance. The node of the jointed reed represents the attack in the spring, and the internode the intermission between attacks. The internode is longer than the node, and the intermission longer than the attack. To carry the figure further, the ten-foot cane is divided into proximal, middle, and distal parts, each in turn formed of several nodes and internodes. Chronic pellagra is divided into degrees of initiation corresponding to the clinical stage of dyspepsia, the degree of confirmation corresponding to the clinical stage of neurasthenia, the degree of *desperation* corresponding to the clinical stage of cachexia, and each of these three degrees or stages consists of periodic attacks and interperiodic intermissions.

To use Cabot's phrase, the presenting symptom in the initial stage is dyspepsia, the presenting symptom in the confirmed stage is neurasthenia, and the presenting symptom in the desperate condition of the late chronic pellagra is cachexia. These stages lap like shingles on a roof, and, while it is no great matter for the physician to tell which stage confronts him in the pellagrin, it is altogether difficult to know when and where one ends and the next stage begins. The fundamental idea in chronic pellagra is progression, and these stages are epochs in this progress. It is natural that they should vary very much in time, but as a rule the duration decreases from first to last; the dyspeptic stage may last for fifteen years, and then be short of its full development.

A symptom that is temporary in one stage may become permanent in the next and of increasing intensity. Temporary neurasthenia often appears in the attack of the first stage, but permanent neurasthenia is the marked symptom of the confirmed degree. Diarrhea is temporary in the dyspeptic time, longer in the neurasthenic stage, and practically continuous in the shorter cachectic forms. Emaciation presents itself in the attacks during the second stage, but there is usually a gain in weight in the intermission following;

emaciation is, however, constant in the cachectic time and of distressing permanency. In America these facts are not so evident because here the disease is as yet more strikingly temporary in time and severe in its aggregate symptoms, and therefore the presenting symptoms of the different stages and the evolution of a symptom through the course of the disease is less apparent. Nevertheless, each stage of chronic pellagra is an aggregate of more or less well-defined symptoms, and the course of the disease progresses by the evolution and increasing intensity of these symptoms.

The initial stage marks the beginning of the disease, and years may elapse before the disease gains appreciable foothold. Several years may elapse without an attack, and then suddenly a more severe attack develops, with the subsequent appearance of the neurasthenic stage. Indeed, the confirmed degree may be less serious than the initial degree, and the feebleness of the supposed oncoming cachexia never develop. Instead of progressive seriousness, there may occur a progressive lessening of the symptoms. The symptoms of the first and second stages may occur at the same time, and, as very frequently happens, the second and third stages seem to be identical. In this country the initial stage and simple dyspepsia in many cases fail to appear, and the first spring attack ushers the pellagrin into a state of confirmed neurasthenia.

In older pellagrins one is often called upon to distinguish different diseases and their effects from a superimposed pellagra with its inroads, and, while the diagnosis of the different diseases may be easy, the relative effects are difficult. The following case illustrates this:

A white man, 58 years old, developed in 1909 a severe attack of articular rheumatism. He was in bed for three months and recovered from the attack, but with hypertrophic arthritis in both ankles. He had been a farmer, but, on account of his feebleness, went to work in a cotton mill in a small town. In August of 1911 he developed a typical pellagra, with dyspepsia, dermatitis, but practically no dermotagra. I saw him in November, and, from his description of his pellagrous attack and present symptoms, I judged the attack was mild and initial in degree. He was a neurasthenic of a most confirmed type, his heart sounds were weak, and a blowing mitral alternated with a loud aortic regurgitant. He had evidently suffered with a late endocarditis of rheumatic origin from the weakness and evident roughness of all the valvular

sounds. Severe arteriosclerosis was present, and his urine showed hyalin and granular casts, with a large amount of indican. The evolution, in order, was probably arteriosclerosis, aortic insufficiency, Brightism, rheumatism with chronic arthritis, endocarditis, and pellagra over it all. He looked as if cachexia was imminent, and yet the pellagrous attack was mild, and it would be impossible to state accurately the part pellagra played in causing his condition, or to what degree the pellagra had attained. According to him, this was the first attack, but earlier attacks may have been so slight that they were not noticed, or the lowered vitality following rheumatism and endocarditis may have floated a latent pellagra.

1. Initial Degree—Stage of Dyspepsia.—Duration, from one to twenty years. It consists of one or two attacks in the year; usually the spring attack is persistent, and the autumn attack is not constant. With two yearly attacks, the progress of the disease is faster, and the duration of this stage shorter. The attack has been described, but in this stage it tends to be mild, and may last but a week, and averages from four to six weeks. It may be so mild as to pass unnoticed, and this may occur several years in succession before it is severe enough to arouse the suspicion of the patient. The dermatitis in the first few years may be considered a sunburn, especially in those cases in which the general health is unimpaired, and the usual work and play are not interfered with. The appetite is good, except in the height of the attack in the marked cases. In the majority of pellagrins the bowels tend to relaxation, more during the attack and less in the intermission, but constipation occurs, and often the bowels may be normal throughout the early part of this state. Dyspepsia, bulimia, gas in the intestines, are usually present at various times, and especially during the beginning of the spring attack. The dyspepsia is apt to be more noticed than the dermatitis. Belching occurs, the pellagra tongue as heretofore described, occasional abdominal pain, and perhaps weakness and vertigo, especially in the attack. After the attack and during the fall and winter the skin is frequently apparently normal, and often one is unable, except on very close observation, to note any evidence that the dermatitis has ever been present. At times, and more frequently after several attacks, the dermatitis area is slightly darker and more pigmented than normal, and the elbows a little rough.

Weight may continue as usual, with the loss of a few pounds during the annual attack, which, however, is quickly regained. During the summer, fall, and winter, with the absence of the autumnal recurrence, health and spirits are good, and the spring malaise considered natural and to be expected as peculiar to the patient's constitution. At one time of the year the patient feels bad, but he may think this is due to spring and not to disease. Toward the close of this stage, in America from three to five years as a rule, symptoms of neurasthenia begin to creep in, less work is done, headache comes, the spirits lack buoyancy, and the walk is not so rapid and elastic. Mental activity lessens, and the mild malady of the first stage begins to be succeeded by the more confirmed degree of the neurasthenic time.

2. Confirmed Degree—Stage of Neurasthenia.—Duration, from one to ten years; in America usually less than five years. The attacks of this stage differ from those of the dyspeptic stage, in degree rather than in quality, and in the aggravation of the symptoms of the first rather than the introduction of new symptoms. The attacks are certainly more severe, last longer, recovery from them is slower, and their permanent results strike deeper into the mental and physical strength. In the language of Mayr in Hebra's Treatise, "the fresh symptoms which now present themselves do not concern the eruption, but rather indicate the progress of the internal malady." The cutaneous involvement pursues a beaten track throughout the course of chronic pellagra, while the new symptoms refer to the greater involvement of the nervous system and the appearance of symptoms which are signs of this new and more serious turn of the disease. Here one is tempted to ask what part of the new symptoms is due to organic changes in the nervous system and what part to the aggravation of the condition of the alimentary tract and the resulting effect on the general nutrition. The great difference in the two stages is not in the attacks in the spring or fall, but in the marked difference in the pellagrin between the attacks. In the intermission of the dyspeptic stage he is apparently and practically well; in the second stage he is a confirmed neurasthenic all the time, and his normal metabolism begins to waver. The attack is more severe, and in the intermission he is more feeble.

Loss of flesh is permanent, the forehead becomes wrinkled, the senile face is in evidence, the body is bent, and the walk is aged;

he leans on a stiek; at times he staggers and his legs are drunk. Weakness of the muscles is evident, fatigue comes after little exertion, and between attacks the eondition of the pellagrin reminds one of Beard's description of a neurasthenie in his "Nervous Exhaustion:" "Unwonted and unaccustomed muscular exercise is especially irksome to neurasthenie sufferers. They can do very well in an ordinary routine, but stepping out of this routine, and attempting something new to them, they quickly become wearied. The very narrow margin of muscular force is soon exhausted. This applies to both nervous and muscular exhaustion." Later in this stage develop tremor, cramps, contractures, cataleptic and epileptic states, tetanic movements, tendencies to fall in all directions, uncertainty in all things.

The tongue in the attaeks is more inflamed, stomatitis more severe, even for a few days it may interfere with swallowing; nausea, pyrosia, intense bulimia, real gastralgia, recurrent epigastric pain that brings the gastrie crises of tabes to mind; drooling saliva during the attack and occasionally during the intermission; increased number of stools during the attack, with a moldy odor; abdominal distention increased after eating, voracious appetite or refusal of food; a diarrhea that alternates with a constipation, or that continues intermittently, or even persistent constipation, tenesmus, gastritis, enteritis, and rectitis that vary in severity and in persistency. Both Strambio and Roussel considered the sudden attacks of diarrhea or vomiting that occur at this stage to be due to spasmodic phenomena arising from the nervous system.

The pulse is more rapid, running often in the intermissions from 80 to 100; dyspnea may develop, and occasionally slight dropsy, though these are not common in Ameriea. The reflexes are usually permanently exaggerated, vertigo, headache, heavy-headedness, drawing feelings in the back of the neck, pain in the back to one or the other side of the dorsal spine, and all or any of these absent at times; and, like a neurasthenic, a sense of well-being and health alternates with nerve exhaustion and all the symptoms of the nervous dyspeptic. The mind loses its cunning; no more is it the active human mind. Little tasks become like mountains, and the pellagrin is more content to sit and rest than to walk and work. Like Napoleon in his last days, he prefers rest to all the thrones of Europe.

The hand is now no longer a normal hand. Even in the intermissions its back is pigmented, the wrists are dark with a brownish-red color, and occasionally it has rounded to the front; the elbows are rough and the skin over them becomes thick; the knees are rough likewise, and even the feet and shins are sometimes darker than normal. Areas of dermatosis of the face or neck are now unusually dry and branny, and one often involuntarily thinks of dry, scaly eczema. The finger and toe tips seem pink and clean; the face rather reddish like a faint blush, or of a darker bronze like that of a bronzed diabetic. One man had this red hue over his back and between the anal folds. The hands, legs, and feet burn at times to despair, itching may alternate with burning, and the physician is asked to "give a remedy that will stop this burning and let me sleep." The skin over the hands cracks, and is loose and wrinkled like the senile skin. The recurrent dermatitis has left an old man's hand.

The urine is usually acid; the specific gravity may be normal, but is often lowered, and, according to Procopiu, gives in some cases the diazo reaction. The amount of urine is increased, with occasional traces of albuminuria and a few casts. Sight begins to fail, and reading is troublesome to the eyes and burdensome to the mind. The neurasthenic is naturally a sad person, and despondency, fear of water or attraction to it, desire to suicide, days of melancholia and despair, mark the wane of the mind, oncoming cachexia, and insanity.

3. Degree of Desperation—Stage of Cachexia.—Duration, from one to five years, usually short. Dermatosis and dyspepsia characterize the initial time; dermatosis, indigestion, neurasthenia, and feebleness the confirmed time, and all these, with prostration, cachexia, and insanity added, occur in the degree of desperation. Death may occur early, or insanity develop and the pellagrin, with his pellagrous insanity and some cachectic symptoms, live many years. It is well to understand that pellagrous insanity may occur in the neurasthenic stage as well as in the last stage. Insanity in pellagra may come at any time. To walk through any asylum for the insane in the southern states and see the pellagrins is ample proof of this. At Mombello, in Italy, I saw two pellagrins with manic-depressive insanity, who weighed probably 160 pounds each, were well and strong physically, and yet whose minds were gone in the initial stage. Dr. Green showed me at the

Georgia asylum a negro of this type, who looked well nourished enough to do a day's work.

Invalidism is the rule here. Paralysis, paraplegia, and hemiplegia occur, though anesthetic areas are rare. Ankle clonus and the Babinski reflex may be present, and absence or presence of knee jerks. The delirium and diarrhea may alternate.

Diarrhea may become blood-streaked, mucus is found in the stools, and a serous diarrhea, unyielding to any treatment, end in death. The hands are exceedingly thin, peteehiæ may occur, and discolored spots as if the flesh had been bruised; the muscles atrophy and the subcutaneous fat is gone. Bed sores may develop, there is incontinence of feces and urine, and the gradual onset of acute terminal pellagra, with high fever and death. The discussion of pellagrous insanity will be found in the chapter on "Nervous System," page 171.

PELLAGRA SINE EXANTHEMATA.

I have in this month seen the patient described as Case 1, on page 18. The skin symptoms were absent, and only a long experience with pellagrins would permit one to suspect a past pellagrous dermatosis. The pellagra tongue was present and occasional diarrhea. Strambio believed that the skin symptoms could be absent during the entire course of chronic pellagra, including even in the spring attack, and to this condition Strambio gave the name of pellagra sine pellagra. He applied this phrase to the permanent absence of skin symptoms in pellagra, and not to the temporary absence during the annual intermission following the annual attack. Girelli, of Brescia, cited a case with violent pellagrous symptoms of twenty years' standing and no dermatosis. Roussel cites two cases.

The phrase is misleading, and, literally translated, is "pellagra without pellagra." I have substituted for this a plainer phrase, and one that means just what it is intended to mean—pellagra sine exanthemata, or pellagra without the exanthem. Strambio's phrase means pellagra without pellagra, whereas he meant that a marked pellagra does exist, but no skin involvement. It is probable that this condition does exist, but that it is very rare. The exanthem is coincident with the attack, as the erythema of scarlet fever is coincident with its attack; the pellagrous exanthem marks

the exacerbation time of pellagra, and in this time it can certainly be absent and the internal malady be present. It is probable that a more careful study of the skin will show a pellagrous dermotagra in these cases, with absence of the dermatitis. A sharp distinction is to be drawn between these, for in the past the attention has been focused nearly altogether on the dermatitis. I have under observation at this time a female pellagrin who, I know, has pellagra, and yet there has never been a dermatitis, but a noticeable dermotagra exists in the region of the elbows, on the flexor surface of the forearm, and at variable times on the back of the hands. When her tongue and diarrhea grow worse, the dermotagra increases. Harris describes three cases of pellagra sine exanthemata in the *American Journal of the Medical Sciences* for May, 1911. One should be very careful, and hesitate a long time before he makes a diagnosis of this form. I would prefer to observe such a patient several months before reaching a conclusion in my own mind. In the meantime treatment for pellagra could be instituted if the pellagrous evidence was weighty.

PSEUDO-PELLAGRA.

It was an unfortunate day when Roussel applied the term pseudo-pellagra to pellagra. There is no pseudo-pellagra. Real pellagra is hard enough for a patient to suffer and for the physician to treat, and the use of pseudo in regard to the disease is unwise. A disease is either pellagra or it is not pellagra, and there is no middle ground. Pseudo-pellagra is not pellagra; it is some other disease. Pellagra is pellagra, and there is nothing false about it. Roussel applied the term more in derision of imagined and arbitrarily constructed groups of symptoms, which he called *unites factices,* in patients not pellagrous. Billod believed in pseudo-pellagra, and executed many marked diagnostic flounders; Hardy confused pellagra and alcoholism; sporadic pellagra was unexplained and called pseudo-pellagra; pellagrins who had never eaten corn in any form, but who had pellagra, were called pseudo-pellagrins. Because a confirmed alcoholic has a few nerve or digestive symptoms that pellagrins have is no reason to call him a pseudo-pellagrin. When pellagra invades a country for the first time, inexperience on the part of some and fear on the part of others inclines to confusion in a few cases as to just what does

constitute the pellagrous syndrome, and occasionally the diagnosis of pellagra is made without evidence and incorrectly. Referring to these conditions in France and the different maladies called pellagra and pseudo-pellagra, Dejeanne wrote: "These are maladies differing widely among themselves, and all of them differing widely from endemic pellagra, not only in the etiology, but also in the nature and concatenation of the symptoms."

CHAPTER IV.

THE ALIMENTARY TRACT IN PELLAGRA.

In Edmond About's novel, "Maitre Pierre," whose scenes are laid in the Landes in France, and which was published in 1844, the heroine says of pellagra: "It commences in the stomach and soon reaches the surface like a noxious weed which flourishes rankly everywhere." When the cause of pellagra is fully known, the reason for the extensive involvement of the gastrointestinal tract will become evident. As a rule, the symptoms that arise here are the earliest, the most persistent, and the most dangerous of all the pellagrous symptoms; and of these pellagrous symptoms, diarrhea holds the red flag, and reminds one of Lauder Brunton's statement that "diarrhea destroys more lives than any other disease." The two great causes of gastrointestinal irritation are (1) those which concern the food and (2) those which concern the organism, and in the latter class pellagra is found. I am disposed to believe that for some reason the gastrointestinal tract should blame the nervous system for much of its condition in pellagra. Goodhart, quoted by Allbutt, writes: "It is no great exaggeration to say that there are only two forms of indigestion—that produced by overeating and drinking, and that due to a failure of the nervous power." The nervous power fails, and the gastrointestinal condition keeps pace with this failure.

These symptoms involve the oral cavity—always the tongue, the pharynx, the esophagus, the stomach, the large and small intestines, the salivary glands, the liver, pancreas, and spleen. There are organic and functional changes, and both to a marked degree. Stomatitis, ptyalism, glossitis, pharyngitis, esophagitis, gastritis and dyspepsia, enteritis and ulceration are in one sense the different and separate diseases whose union with variations present the extensive pathology of the digestive system. With a few slight changes, Lauder Brunton's description of dyspepsia applies to the mass of symptoms of indigestion in pellagra: "Briefly, the symptoms of dyspepsia are a furred tongue, a bad taste in the mouth,

want of appetite or even loathing of food, vomiting, oppression in the chest, weight at the epigastrium, pain, distention, flatulence, acidity, eructations, pyrosis, constipation or diarrhea."

THE TONGUE.

The condition of the tongue is the most constant and most important diagnostic symptom furnished by the digestive system. During the onset of the attack it is furred and coated, and the patient has occasional anorexia and bad breath. As the outbreak occurs, the lingual epithelium is lost, the tongue becomes red, is slightly swollen, and the tip and anterior lateral margins are first affected and then the back. Irregular fissures form in the middle and on the lateral margins; these sometimes cross the tongue and descend the sides like the outline of a cross section of an empty shoe box turned upside down. This stage is a dissecting glossitis. The true pellagra tongue is a tongue without a coat, the beet tongue —the "bald" tongue of Sandwith. Aphthous ulcers may develop on the tip and margins, and their rawness causes pain in eating. As the attack recedes, the tongue for a long period may present a few red papillæ scattered over the tip, and the epithelium may never return with its characteristic thickness.

This redness of the tongue is due to inflammation, and for a time after the attack the tongue may present a paleness due to anemia. This pallor is out of all proportion to the previous redness and fissured condition. The tongue improves as the attack recedes and inflames as the attack approaches, reaching the greatest inflammation at the acme of the outbreak. In the severe cases it is often tremulous, usually thick and beefy, and occasionally pointed. Occasionally the papillæ may be dark at their tips, due probably to swelling with cyanosis. Sandwith's 163 cases had tip and edges naked and red in one-half the number, one-fourth completely denuded of epithelium, and only 5 had a coated tongue; 37 were normal except for anemic pallor. Of 121 patients with tongue either completely or partially denuded on leaving hospital, 45 returned as normal, and 38 remained partially denuded. As a rule, during the onset the tongue is coated, then gradually loses its coat, and the papillæ at tip appear red and prominent; during the outbreak the tongue is red, fissured, and its coat gradually reappears as the attack recedes. During the periods of intermis-

sion the tongue may be strangely clean, unless one thinks of pellagra. It is well to remember that after surgical procedures in septic cases the tongue may be naked, red, and swollen, with accompanying stomatitis; and in uremia the tip of the tongue may be similar to the pellagrous tongue. Acute alcoholism presents the inflamed tip, prominent papillæ, and tender margins.

GUMS, TEETH, BUCCAL MUCOSA, PALATE.

Between attacks the gums are usually normal, but during the outbreak the gums are inflamed in common with the rest of the oral mucosa. They are tender, often spongy and easy to bleed, as in scurvy; around the lower incisors this condition is most noticeable. The teeth are not affected, and in one series out of 166 pellagrins 120 had sound teeth. Pellagrins usually can masticate well, and with them the teeth do not in any way influence the gastrointestinal condition. The poison arises within in pellagra.

Between the attacks, except in the subchronic cachectic form where there is no real intermission, the buccal mucosa is usually normal. During the outbreak stomatitis is present, and reaches its acme at the culmination of the dermatitis and the glossitis. At this time the outer border of the lips are dry, and, in the severe cases, of a cyanotic hue; the inner border of the lips and cheeks are red, tender, raw, and swollen, and this inflammation extends over the buccal mucosa to such an extent that eating and swallowing are difficult, and even weak acid drinks are so painful and burning that they can not be taken. Occasionally Stenson's duct opens into a pit, instead of on the surface, on account of the swollen mucosa. Aphthous ulcers are common, and occasionally small blisters arise on the inside of the cheeks, which, when burst, leave the membrane dead and pale. These small bullæ are especially noticeable as the period of recession begins. At this time the mucosa exfoliates, and is thrown off in macerated strands. In the very mild attacks the mucosa is only red and may be tender for a few days, but it lacks the velvety rawness of the severe forms.

The latter half of the palate, including the uvula, the anterior and posterior pillars of the fauces, may be either red in the lighter attacks, inflamed on the anterior pillars, with scattered pin-point

areas in the more severe attacks, and entirely raw, very red, and even ulcerated on the anterior pillars in the severe forms. The uvula may become edematous, sag, and add to the general pharyngeal discomfort. Posteriorly the inflammation is neither as severe nor as uniform as anteriorly in the region of the labial frenum. Evidences of the oncoming stomatitis are first found anteriorly around the frenum, and it persists longer there. The actual stomatitis does not last longer than two weeks as a rule, and may cause inconvenience for only two or three days. As the attack recedes, the increased saliva decreases, the edema departs, the epithelial coverings regenerate, and the mouth feels and appears normal.

SALIVARY GLANDS.

Ptyalism is a variable symptom, depending on the degree of stomatitis present, and on an unknown factor in that a few cases present during the attack an almost continuous drooling of saliva from the mouth and an increased expectoration in the intermissions. One old lady of 60 years had a constant flow of saliva for three weeks, and then, when up and feeling well, stomatitis gone, she would have to spit about every fifteen minutes during her waking hours. Just why this extraordinary symptom should continue I do not know. The increase synchronous with the stomatitis is primarily a reflex stimulation of the salivary and mucous glands, but it is also influenced by the hyperemia, degeneration, and inflammation of the buccal mucosa. There is another factor than the stomatitis, because many pellagrins with severe stomatitis have only a small temporary increase in the saliva. There is present in these cases an abnormal chemical reaction of some kind, as proved by the fact that the saliva may be acid instead of alkaline. Taste may be disagreeable, and even salty or briny, giving rise to the Italian synonym of *pellagra salso* and *umor salso,* or saltiness and salty phlegm. I saw one patient who had a drooling saliva for more than a month, and who died from exhaustion. Swint and Echols at Milledgeville showed me two female pellagrins, insane, dementia precox type, who were up and walking around with a constant production of thick, ropy strands of saliva flowing to such an extent that their garments were wet all the time. It has seemed that in those cases where the saliva was markedly in-

creased the diarrhea was less, and with decreased saliva there was an increase in the severity of the diarrhea. It seems that the body in pellagra is trying to get rid of something, and either diarrhea or salivation may remove it.

Sandwith found 6 out of 151 cases with a bilateral enlargement of the parotid gland. It occurs in children with the bald tongue, and dermatosis on face, ears, and neck. The parotitis is painless, and, like mumps, does not proceed to suppuration. With the dermatitis at its height on the hands, the epitrochlear glands may become enlarged; and with the cutaneous involvement on the face and neck, through the lymphatics, the parotid gland may similarly enlarge. Certainly a far different process is present, because in mumps there is a tendency to a decrease in the saliva. The pellagrous saliva, increased in amount, is deficient in solids, and contains microscopically enormous numbers of enlarged flat epithelial cells, with debris from the tongue, teeth, and buccal mucosa. The parotid gland in the sheep secretes saliva continually, and a similar ability is certainly present in a few pellagrins, leading to the belief that the pellagrous toxin must influence the salivary center in the medulla, as all three pairs of salivary glands are affected.

PHARYNGITIS AND ESOPHAGITIS.

Inflammation of the pharnyx and esophagus is simply a continuation of the pellagrous process. As the stomatitis grows worse, the sensation of rawness in the throat and esophagus increases, and also the pain in swallowing. I have seen a female pellagrin attempt to drink an orange albumen and complain that "it burns all the way down." The esophagitis can not be caused by the condition of the gastric juice, because the acidity is decreased and gastric regurgitation would therefore play no part. The throat and esophagus grow worse as the stomatitis increases, and better as the stomatitis improves. These symptoms exist only during the attack, and cause inconvenience chiefly during the period of outbreak. During recession, regeneration and healing of the mucosa is rapid.

STOMACH AND INTESTINES.

In these organs arise such symptoms as gastralgia, epigastric pain, bulimia, nausea, vomiting, gaseous distention, diarrhea, en-

teritis, colitis, and rectitis. Burning in the stomach or pyrosis is a variable symptom, present chiefly during the period of outbreak. Nausea is common and actual vomiting absent in the milder cases; during severe attacks vomiting is a common symptom. The pellagrin sums up his gastrointestinal symptoms as **sore mouth, indigestion,** and **diarrhea.** Of these indigestion, lack of appetite, coated tongue appear first, next the diarrhea, and lastly the sore mouth. Even with those patients who say that the dermatosis is first, careful and patient questioning will reveal a week or a few days of heaviness in the stomach, gas, belching, occasional nausea, and that disease known far and wide as "biliousness" may have preceded the dermatitis. J. Clarence Johnson, in his 1911 paper before the American Gastro-Enterological Association, presents the analysis of 20 cases and relates the analyses of the stomach contents, the position of the stomach, the diarrhea, to each other and more general symptoms. This table (page 113) adds much new information to the condition of the stomach and intestines in pellagra, and on the relation between the secretion of hydrochloric acid and the diarrhea.

Summarizing the important details of this valuable table, the stomach was normal in position in 11 cases, ptosis present in 4, and atony in 5; nausea was present in 15, vomiting in 7, indicating a common experience that vomiting is rather the exception and present only during the severe cases, or during the acme of the outbreak. I have never seen it except in bed-ridden pellagrins, and in fatal cases the vomiting is often an accompaniment of the diarrhea. Only 3 of the 20 cases failed to have pain in the stomach, the gastralgia so accented by Procopiu and Triller. The three sensory gastric symptoms in pellagra are pyrosis or burning, gastralgia or a real gastric hurt, and bulimia or the hungerache. The pyrosis is rather the most chronic symptom of the three, often preceding the other gastric symptoms and persisting during the winter when the others have disappeared. These burning pains are probably referred pains, having a common cause of origin with the well-known fiery sensations in the hands and feet. I can not believe that they arise in the stomach from any gastric condition, but are rather due to cord involvement and impulses reflected through the sympathetic ganglia.

The gastralgia may arise without known cause, persist for a few days, and disappear. It is rather more chronic than the

Analysis of Stomach and Intestines in Pellagra.

	Age	Sex	Occupation	Previous history	Duration	First symptom	Nausea	Vomiting	Pain in stomach	Diarrhea	Loss in weight	Dizziness	Cough	Profuse saliva	Ocular symptoms	Heart	Lungs	Liver	Kidneys	Stomach	Test meal	Fecal examination	Eruption
1	64	Male	Farmer	Neg.	2 mos.	Dizziness	+	+	+	+	+	+	+	+	−					Situ	Hcl—R—	Nothing not found in ordinary diarrhea and dysentery.	Mouth and hands
2	52	Female	Housewife	Neg.	4 mos.	Diarrhea	−	−	+	+	+	+	−	−	−					Atony	Hcl—R +		Palms of hands
3	39	Male	Merchant	Indig'n	?	Indigestion	+	−	+	+	+	+	−	−	−					Situ	Hcl—R—		Face and hands
4	40	Male	Farmer	Neg.	2 yrs.	Pain	+	+	+	+	+	+	−	+	−					Situ	Hcl—R +		Face, hands, mouth
5	36	Male	Lawyer	Indig'n	2 mos	Pain	−	−	+	+	+	+	−	+	−					Situ	Hcl—R +		Hands and mouth
6	35	Female	Housewife	Indig'n	1 yr.	Pain	+	−	+	−	+	+	+	−	−					Situ	G+F 36 T 66		Hands
7	65	Male	Minister	Neg.	6 wks.	Pain	+	−	+	−	+	+	−	−	−					Situ	G+F 38 T 74		Hands, arms, legs
8	48	Female	Housewife	?	2 yrs.	Choking	−	−	+	+	+	+	+	−	−					Ptosis	Hcl—R—		Face and hands
9	32	Female	Housewife	Indig'n	1 yr.	Pain	+	+	+	+	+	−	−	−	−					Situ	Hcl—R +		Hands, arms
10	34	Female	Teacher	Neg.	1 mo.	Drawing	+	−	−	−	+	+	−	−	+					Atony	G+F 32 T 50		Hands
11	36	Male	Merchant	Rheum.	2 mos.	Nervous	+	+	+	+	+	−	−	−	−					Situ	Hcl—R +		Hands, arms, face, mouth, body
12	37	Female	Housewife	Indig'n	2 mos.	Diarrhea	+	−	+	+	+	−	+	+	−					Situ	Hcl—R +		Hands, wrist, mouth
13	51	Male	Salesman	Diarrh.	1 yr.	Eruption	+	−	+	+	+	−	+	+	−					Ptosis	Hcl—R—		Hands, arm, mouth
14	34	Female	Housewife	Diarrh.	4 yrs.	Diarrhea	−	−	+	+	+	−	+	−	+					Situ	G+F 30 T 38		Hands, wrists
15	37	Female	Housewife	Indig'n	2 yrs.	Eruption	+	−	−	−	+	+	−	−	+					Ptosis	G+F 24 T 42		Hands, mouth
16	32	Female	None	Indig'n	3 mos.	Eruption	−	−	+	−	+	+	+	−	+					Atony	G—F 18—T 38		Hands, mouth
17	26	Female	Housewife	?	6 mos.	Sore mouth	+	−	−	+	+	−	+	+	−					Atony	Hcl—R +		Hands, mouth
18	28	Female	Housewife	T. B.	?	?	+	+	+	+	+	+	+	−	−					Atony	Hcl—R—		Hands, mouth
19	47	Male	Merchant	Neg.	8 mos.	Indigestion	+	+	+	+	+	−	+	+	−					Situ	Hcl—R—		Hands, arms, mouth
20	52	Female	Housewife	Indig'n	1 yr.	Diarrhea	+	+	+	+	+	−	+	+	−					Ptosis	Hcl—R—		Hands

Normal except myasthenia in 11 and 12

Normal except tuberculosis in 18

Normal except large in 8 and 11

Normal except albuminuria in 11

Hcl, hydrochloric acid; R, rennin; F, free; T, total acid; G, Gunzburg's test. From "The Alimentary Tract in Pellagra," by J. Clarence Johnson. (Transactions American Gastro-Enterological Association, 1911.)

bulimia, and is not influenced by food. Indeed, the distinguishing characteristic of these sensory symptoms is that they seem to bear no relation to food in any way. Pellagrins with severe gastric symptoms often suffer as much with an empty stomach as with regular diet. As one of them wisely said, "I have pain in my stomach and indigestion, whether I eat anything or not."

With these sensory symptoms, varying in kind and in degree, nausea, and often increased saliva, it is no wonder that choking sensations and difficulty in swallowing are present at times. The pellagrin remarks that he can drink just so much water—to drink

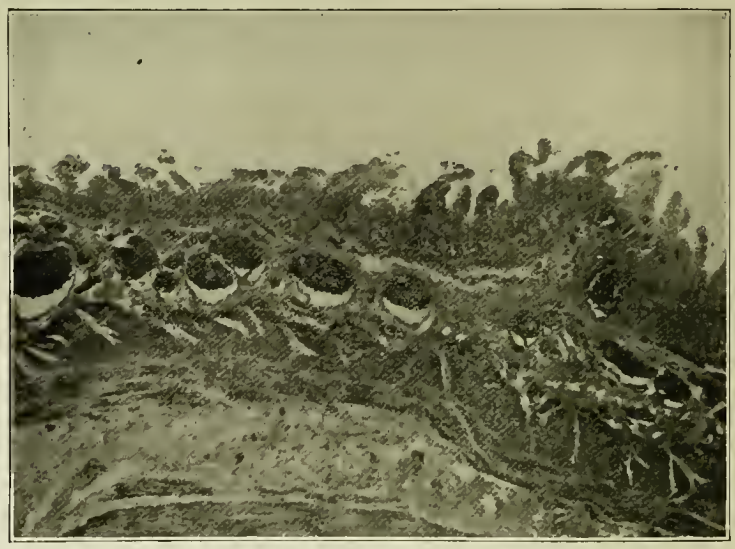


Fig. 16.—Intestines showing atrophy of the muscles; increase in the connective tissue; chronic enteritis; hematoxylin-eosin. (By Dr. Bravetta.)

any more will choke him, or only so much will run down. The nervous exhaustion marked in the outbreak, added to these sensations of choking and burning, with gaseous distention, often causes the complaint that the stomach is full and weighty even when no food or drink has been taken for hours. Cough was present in 11 cases, and one of these was tubercular. With stomatitis and pharyngitis, nausea, and other gastric symptoms, the wonder is that cough is not more common and more violent. Unless a local pulmonary condition is present, it does not persist after the attack is over.

One of the most striking facts in this series of cases is the fact that there seems to be a relation between the lack of hydrochloric acid and the presence of diarrhea. Only 6 had free acid, and, with one exception, diarrhea was absent; in the 14 with absence of hydrochloric acid there was diarrhea. The diarrhea in the one exception noted was temporary and due to a different cause. Rennin was present in 7 cases, and in those cases with rennin present and the acid absent, Johnson noticed that the "diarrhea was less frequent, less severe, and less persistent." Another striking fact is that in no case with free acid has insanity developed or death followed in his experience. Two cases had no gastric juice whatever; in one was pain, frothy saliva, vomiting, diarrhea, and prostration; in the other a persistent diarrhea, with dizziness and ocular symptoms "without astigmatism." Johnson's argument as to the relation of acid absence and diarrhea is confirmed by the ordinary observation that in pellagrins, when the stomatitis and esophagitis permit, the administration of hydrochloric acid with pepsin has more effect on the diarrhea than the ordinary astringents and diarrhea remedies.

Back of the absence of the acid stands another problem—What causes the lack of acid? What causes the involvement of the alimentary tract as a whole? Is it related to the nervous system as an effect, or is it as truly an outcrop of the pellagrous process as the dermatosis or the pellagrous neurosis and organic cord changes. If the diarrhea is the result of gastric failure, is the gastric failure due to a deeper failure of the nerve centers? How much are the sympathetic ganglia in the abdomen involved in all this? Are they primarily affected as Lombroso thought, or is it not rather more in harmony with the facts to consider the sympathetic ganglia as the playground and meeting place of two different sets of impulses—one arising in the cord as the result of the pellagrous process, and the other in the alimentary tract as the result of the pellagrous process there? One is reminded of the striking statement of Gurd that pellagra is essentially a disease of the epithelial tissues, including the skin epithelium, the alimentary endothelium, and the ectodermically derived nervous system.

Out of all these questions and facts emerges one clear conclusion—changes in the nervous system in pellagra can not be considered solely responsible for all the symptoms that in an ordinary

case of neurasthenia are attributed to nerve exhaustion. The stomatitis, indigestion, gastritis, diarrhea, gastralgia, ravenous appetite, or refusal of food, thirst, or antipathy to water will of themselves cause dizziness, vertigo, weakness, neurasthenic conditions, functional ocular symptoms, and the exhaustion common to constant nausea and occasional vomiting. One recalls how great an influence a single aphthous ulcer has on his feelings, indigestion following a banquet provokes irritability and the blues, diarrhea for a day calls for rest, and the combination and increased severity of all these in pellagra produces a reflex effect on the nervous system and systemic condition that contributes to the facies dolorosa of the pellagrin.

The diarrhea usually precedes the dermatitis, but it may occur simultaneously, and Fritz has noticed that it is common for the two to appear together in those whose work keeps them in the sun. It also shows that the diarrhea is the symptom of a systemic morbid process. The diarrhea, stomatitis, and dermatitis reach their culmination together during the outbreak. The diarrhea comes gradually, lasts about a month all told, disappearing gradually as it came. In Tucker's 55 collected cases diarrhea was present in 54, with remissions in the diarrhea in 36 cases, and diarrhea alternating with constipation in 30 cases. All my cases except one had diarrhea, and, without exception, the more severe the diarrhea the greater the prostration and exhaustion, and the more apparently severe the pellagra. In some pellagrins the flux is so severe as to merit the title of diarrheic pellagra. The Egyptian cases of Sandwith seem to have less diarrhea than either the Italian or American. Out of 166 cases the bowels in 103 were normal, 9 had slight constipation, 46 with slight diarrhea, and 8 with excessive diarrhea.

In the height of the spring attack the number of stools in the twenty-four hours varies from six to thirty, ten to twenty being an average. In my own experience the number of stools is influenced neither by rest nor food, and the number is as great in the night as in the day, and often worse from 3 to 9 o'clock in the morning. In the early part of the attack and in the initial stage of the disease the diarrhea is more spasmodic in character and with far more peristaltic activity, so that the patient complains of abdominal pain and griping like a colic from indigestion. The stools at this time are thicker, contain more mucous and endothelial cells,

the pellagrous odor is not so pervasive, and the stools do not come so freely as in the latter stages. At this time they may be tinged with blood, though not so commonly as in acute dysentery. They vary from gray and light-brown to green in color.

In the later stages of the disease the diarrhea assumes a more serous character, is more persistent, and far less amenable to treatment. It is almost a pure watery stool, usually of a light-green color, occasionally almost clear. At this time the acute phase of the disease may develop, and the diarrhea precede the delirium, and foreshadows marasmus and the approach of death. As the serous discharges increase, distention develops and paresis of the intestinal walls occurs. Rectitis, hemorrhoids, and anal fissures add to the cachexia and distress. As a rule, the mild cases do not develop a severe diarrhea, and the diarrhea ceases as the attack recedes. The diarrhea may be the only symptom of the fall exacerbation and may last for only a few days; in other cases, after the first spring attack, the bowels are always relaxed, and two to four stools a day common. In the cases with constipation the attack is mild and short, and the disease progresses slowly. The life of the pellagrin is prolonged in inverse proportion to the severity and the persistence of the diarrhea.

As the disease advances, the entire alimentary tract becomes inflamed; gastritis, enteritis, colitis, and rectitis are the foundations for gastric and intestinal ulceration, with blood, mucus, pus, and increased putrefaction and fermentation. At this stage indicanuria is common. Absorption is interfered with, and there is an increase in undigested food materials, especially fats, starch granules, plant cells, and muscle fibers. The stools are acid as a rule and gaseous, looking as if they had been whipped, so numerous are the air bubbles. Under the microscope there is an increase in the fat globules, due probably to a decrease in the bile and pancreatic juice. If the stool in pellagrous diarrhea is put in a bottle or graduate and allowed to stand for several hours, it separates into three layers—(1) above is the aqueous portion, serous in character, often colored a light-yellow; (2) below this a thick gray layer composed of mucus, pus, and occasionally blood cells; (3) a heavy layer below, dark-brown or green in color, and composed chiefly of waste matter from the food, or ordinary fecal matter, in which is found clinging mucus that has not separated. J. D. Long in his admirable studies found ammonium and magnesium

phosphate crystals, fatty acid crystals, calcium oxalate, cholesterin plates, and fungi.

PATHOLOGY.

The mucosa of the oral cavity presents hyperemia, occasional swelling, ulcerated areas, and infrequently the remains of small vesicles. A favorite spot for the vesicles is on the cheek just anterior to the pillars. At times the pharynx, palate, and esophagus may be in this same hyperemic condition, with a diffuse ulceration.

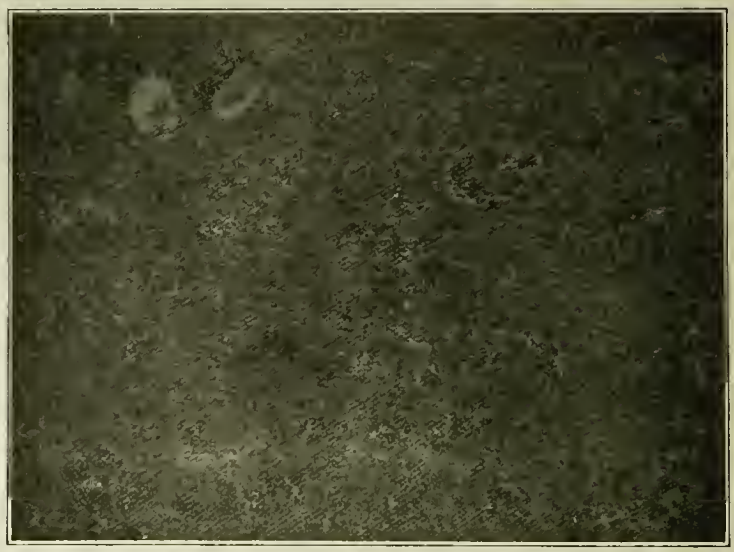


Fig. 17.—Section of liver; hyperemic; hematoxylin orange. (By Dr. Bravetta.)

At the summit of the anterior pillars two cyanosed areas, round or oval in shape, are often found. The tongue presents fissures, absence of its epithelial coat, and engorgement of the veins on the margins and beneath. Ulcers may be present on the tip and anterior lateral margins.

The stomach is found normal in position and size, or gastroptosis occurs, and I believe more frequently than the records would show, and dilatation is present infrequently. Watson reports a case in which there was excessive redness of the peritoneal coat noted during a laparotomy. Post-mortem, the organ is rather pale,

the muscles atrophied, the walls thinned, and the internal walls covered with mucus. In the more acute forms the classic picture of a gastritis is present, with redness of the mucosa and marked ulceration, especially in the pyloric region.

The intestinal changes are variable, depending on the length and the severity of the disease. The intestine is usually emaciated and thinned in proportion to the rest of the body, though it is not true that the walls are always atrophied, especially throughout their entire course. As a rule, the intestine is atrophied, brown pigmentation is often present, and the muscular coat thinner than

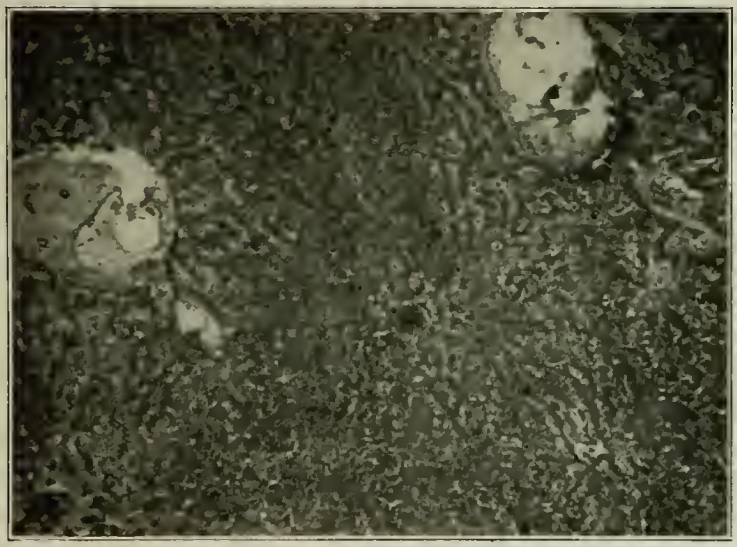


Fig. 18.—Spleen, showing increase in connective tissue; hematoxylin orange. (By Dr. Bravetta.)

normal. Labus thought the intestinal canal was contracted throughout, a point not confirmed altogether by later investigators. With acute cases and enteritis, ulceration may occur at any part of the large or small gut. With ulceration, hyperemia instead of anemia is present in more or less localized sections. Ulcers may form in the duodenum, jejunum, and ileum—more frequently in the last two divisions; ulceration may occur in the large intestine, but most often in the rectum. The mouth and rectum are the most frequent areas in the alimentary tract for pellagrous inflammation. The anus is often swollen, discolored, and fissures and hemorrhoids

are occasionally found. The diarrhea is the cause of these fissures and hemorrhoids, and the resulting irritation.

The liver varies from atrophy to hypertrophy; in far the greater number of cases it is atrophied. This is a simple atrophy due to malnutrition, cachexia, and marasmus. The decrease in size may be very marked, even to one-third the original size. The edges are sharp, the capsule wrinkled, and the gall bladder may project beyond the lower border, often dilated and engorged with bile. Fatty degeneration, cloudy swelling, or brown atrophy may exist in the liver cells. The liver is frequently tough, and pale like the liver in senile anemia. The pancreas is usually small, tough, and friable. The spleen may be normal, but it is usually atrophied and tough. In his report on case 6 of his post-mortems, Strambio notes the spleen weighed twenty-seven pounds, with no other comment. This was probably a malarial spleen, as in all his other cases the organ was normal according to his report. The mesenteric glands are often enlarged.

CHAPTER V.

THE SKIN IN PELLAGRA.

Hebra, in the first volume of his famous work on "Diseases of the Skin," classifies pellagra as a skin disease in the group which he describes as "acute, exudative, but noncontagious dermatosis." He makes a second division which he calls "the polymorphous erythemata," and includes pellagra there, believing it to be not an inflammation of the skin alone, but depending rather on a toxic action affecting the whole organism.

"The symptoms of the erythematous inflammation of the skin consists in rose or blood-red discoloration, disappearing under pressure, and in a slight degree of swelling, caused by serous exudation or edema. In this affection the tension of the skin is inconsiderable, and little or no pain or itching is complained of. Its course is always acute, and its chief peculiarity is that it generally terminates in the absorption of the inflammatory products, followed by deposit of pigment or desquamation of the cuticle. It rarely happens that either vesicles, bullæ, or pustules develop themselves in this form of dermatitis; and there is never any deeply seated suppuration, attended with loss of substance, or followed by the formation of cicatrices. The erythematous inflammation involves only the superficial layers of the cutis, while the phlegmonous involves the whole skin and the connective tissues beneath." (Hebra.)

Howard Fox very wisely believes the red erythema in pellagra to be a true dermatitis, and not a simple erythema. Hebra was of the same mind, and the sooner we come to their belief the better. Fox adds this important statement: "It would seem quite proper to use the term erythema for the first stage of the disease, which resembles an ordinary sunburn and which lasts only a few days. But it seems somewhat anomalous to speak of the entire eruption as an erythema when the erythematous stage is so comparatively insignificant, while the stage of desquamation is so characteristic and of such long duration." In reading a case reported by Turck

occurs this sentence, and, taken with the statement of Fox, the problem of the skin in pellagra will become easy: "Within two weeks after the operation these patches increased in extent, and there was a condition resembling in places a **dry eczema** and in others **an erythema.**" Here is the clue to the whole matter. The pellagrous skin is dimorphous. It is a dermatitis, which is called also the eruption, the erythema, or the pellagrous exanthem. It is also a dermotagra, or a rough skin, which is called the dry

Fig. 19.—Dermatitis on hands. A clear band of skin is shown on left hand where ring was continually worn, and a darker band is shown on ring finger of right hand where ring was occasionally worn, indicating the influence of light. (Courtesy of Dr. C. C. Bass.)

eczema or branny skin of pellagra, or the eczematoid condition of the skin in pellagra. With this idea of a double affection of the skin in pellagra, I think we can trace the origin of some of the early synonyms of the disease. In Spain it was called "mal de la rosa," named from the rose-red inflammation of the hand. In Italy among the common people originated the pellis agra, or rough skin, because the Italians named it from the roughness so markedly apparent above and around the dermatitis and on the elbow and body, and persisting in some cases on the original der-

matitis area. It is a mal de la rosa because it is a rose-red dermatitis; it is a pellis agra because it is a dermotagra or rough skin. The following diagrammatic arrangement permits us to discuss separately the two divisions:

- Dermatosis of pellagra-dimorphous.
  - 1. Dermatitis, or inflamed skin.
    - a. Erythema, maculo-papular.
    - b. Erythema, vesicles and bullæ.
    - c. Fissures.
  - 2. Dermotagra, or rough skin.
    - a. Eczematoid.
    - b. Keratoid.
    - c. Follicular.

In the majority of cases the dermatosis is a dermatitis of the maculo-papular type with the dermotagra of the eczematoid type. The dermatitis with vesicles and bullæ is far less frequent, involves the skin to a greater degree than the first type of dermatitis, and generally indicates a severe pellagrous attack internally. Fissures develop rarely, and the area of inflammation about them is dependent on their length and depth. Taking a pellagrous dermatitis limited to the back of the hands and wrists, and a dermotagra around the borders of the dermatitis and extending up the extensor surface of the forearm to and including the elbow as a type, the order of the development is as follows, as illustrated by a diagram from Merk, slightly altered:

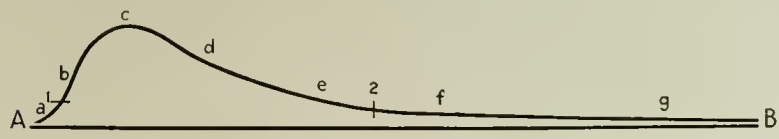


Fig. 20.—Diagram illustrating the development and course of the pellagrous dermatitis.

The beginning of the dermatitis is represented by *a*, when the influx of blood and serum into the dermis is marked; *1* to *2* marks the erythema at the time when the livid red hue is most prominent; *b* represents the increase in the dermatitis, *c* its maximum development, *d* and *e* mark the gradual recession of the dermatitis and the erythema. At *f* the stage of dermatitis may be considered over, and the shedding of the epithelium begins. As the dermatitis recedes, the shed epithelium becomes evident, but, what is important, this continues in fine, branny scales, and marks a permanent change

in the dermatitis area; it becomes hyperplastic, and in a great many cases remains eczematoid, feeling rough and shedding fine scales. This is indicated by *g;* the line *f g* does not again coincide with the basal line of skin smoothness, *A B,* except in mild and rare cases.

Above the wrist and occurring with the dermatitis is the typical

Fig. 21.—Insane pellagrin, with a typical dermotagra in palm of hand. (Courtesy of Dr. Bravetta.)

dermotagra. It involves the flexor surface of the forearm and the elbow-joint over the olecranon process. Usually it is eczematoid in character, partaking in appearance and feeling of a dry, scaly eczema; but there is often a noticeable prominence of the hair follicles, and the elbow may be so rough, wrinkled, and laid off in small rhomboid and rectangular areas that it assumes a keratoid condition. This last is especially true in old cases, and is most

often seen in asylums for the insane. I have seen it both in America and in Italy.

As Watson very wisely remarks, the dermatitis with vesicles and bullæ "differs only in degree" from the maculo-papular type as above. When the vesicles occur, the dermatitis is known as the "wet" form as distinguished from the "dry." Even this wet form differs very much in severity. The dermatitis may be of the ordinary erythematous type, and a few small vesicles may develop in the center of the back of each hand. These are usually small and discrete, contain serum, occasionally blood-streaked. The epi-

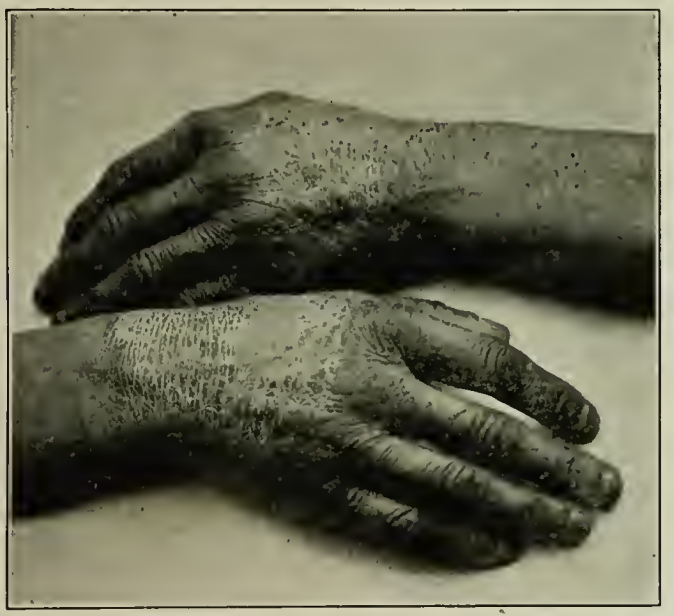


Fig. 22.—Pellagrous dermatitis; dry form, with exfoliation of the skin. (Courtesy of Dr. Bravetta.)

dermis is elevated, serum quickly exudes, and a common blister results. It ruptures, the base is raw, heals quickly, and rarely in the mild forms leaves a scar. In the more severe cases the vesicles become bullæ, cover the back of the hand; edema occurs, and small vesicles may occur on the fingers. On Siler's cases 10 percent had the vesicles, and 66 percent of the cases with vesicles died. The presence of blisters indicates usually a severe attack of the disease. Occasionally they become purulent, with a phlegmonous

involvement of the deeper structures. After rupture, ordinary granular tissue with the small elevations are seen as healing takes place. Either here or in the more severe dry form, fissures may develop, with gaping and localized inflammation. Favorite seats are between the metacarpal bones, over the knuckles, and between the fingers.

The pellagrous dermatosis is a part of the pellagrous process—it is pellagra of the skin. One asks why the skin is affected in pellagra. There is no more an answer to this question than to the other view—why should the skin **not** be affected in pellagra? Measles begin on the face and scarlet fever on the body; the reason is not clear, and one can only say that it is a characteristic of the disease in question. The rose-red spots of typhoid select the abdomen and the dermatitis of pellagra selects the hands, and the selective action of different diseases on different organs and in different locations is as inexplicable as is the specific action of different pathogenic bacteria.

Even with the knowledge that the dermatosis is the skin exhibition of the disease, it is well to remember that the internal malady may continue to exist independently of the eruption or of its disappearance. **When the dermatosis goes, it does not mean that the pellagra has gone.** The eruption does not kill, but pellagra does kill. The dermatosis is the least of the dangers to the pellagrin, but the most important of the symptoms to the physician in diagnosis. It is the passkey and the capstone to the correct diagnosis of the disease. In the language of Roussel, it is the "element decisif dans le diagnostic." The existence of pellagra sine exanthemata is relatively infrequent, and in all ordinary cases of pellagra the decisive element is the dermatosis. It may be so slight as to hardly differ from a slight sunburn and last only a few days in its entirety, though the dermotagra on the forearms and elbows usually lasts longer, but this skin involvement is the decisive and conclusive element in the diagnosis. In the language of Hyde, it is "the local expression of a systemic disorder."

Eruptions in systemic diseases are common, and, viewed in this broad light, there is nothing remarkable in the presence of the pellagrous dermatosis. Syphilis has an eruption, and in suspected cases the physician may postpone treatment and wait for the appearance of the rash, because it is confirmatory and diagnostic rather than

dangerous. Searlet fever, measles, smallpox, and rötheln eaeh furnish their peeuliar rash and eruption, with its individual eharaeteristics, time of appearanee, and duration, and pellagra does

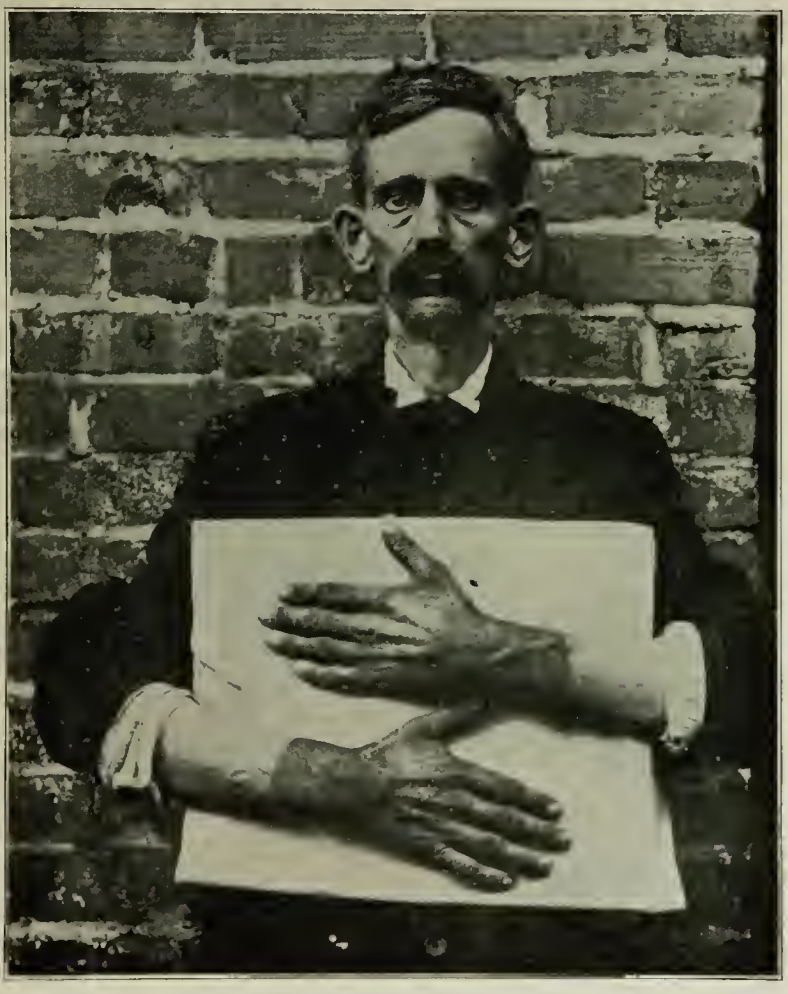


Fig. 23.—Dermatitis. It is symmetrical, and is called the pellagrous glove. (From Pellagra Report of the Tennessee State Board of Health.)

likewise. As Merk well says, "the cutaneous symptoms in pellagra are of the same importanee from the point of view of diagnosis as in chickenpox, smallpox, searlet fever, and measles."

The color of the dermatitis varies according to the stage of the attack and the length of the disease. At the beginning it is the color of red cedar, with a tint of pink added; at the acme of the attack it is the color of red cedar, with a greater and more marked redness; at the decline of the dermatitis it is like red cedar, with a darker tint added. If one takes a smooth piece of the heart of red cedar wood, and compares it with the pellagrous dermatitis, he is at once struck with the similarity and with the fact that the brownish-red color of the cedar is the fundamental color of the various stages of the dermatitis. In the lighter attacks the similarity with sunburn is to be borne in mind, and at times in these mild forms the dermatitis is indistinguishable in tint from ordinary pigmentation caused by the sun. In the more severe forms it turns to sepia toward the close, and especially if there have been several previous attacks. On the face there may be a dermatitis with a marked redness, and at times one thinks of a brick-red color or even the lighter hue of terra-cotta.

In the dermatitis with vesicles and bullæ the redness is more apparent, and in the general development the similarity to a burn first pointed out by Babcock may become evident. These vesicles break and heal, and leave a hard, scabby covering darker than the surrounding skin. During the dermatitis the skin is smooth, glistening and shiny, and may appear tense and very slightly swollen. In the negro the dermatitis is either stark black, like soot or a black hat, or at certain angles a gray tint may be apparent. Marie noticed this gray hue in the Arabs in Egypt. At times this skin in the negro may peel off in large, thick plates, perfectly black in color, and as thick as skin from the sole of the foot of the negro in typhoid. Here the lamellæ are hard and dry, and more like plates than pieces of skin. Ecchymosis may appear on the body during the dermatitis or in the dermatitis area after the exfoliation has begun.

The dermotagra occurs simultaneously with the dermatitis, but usually on the flexor surface of the forearms, elbows, occasionally on the arms, face, and other parts of the body. The branny roughness may be in color and appearance similar to a dry, scaly eczema, except there is usually a brownish tint present and the flexor surface of the forearm and the elbow look dirty as if in need of soap and water. The smooth and glistening appearance of the dermatitis area is absent, and dirty roughness persists. On the

elbow, face, knees, and at times on the trunk even, the slight brownish tint is absent and only the roughness is noticed, with the shedding of small branny scales when rubbed or scratched. I have seen cases in which the maculo-papular dermatitis, after exfoliation and all signs of the inflammation and pigmentation had gone, was sueceeded by a persistent dermotagra on the back of both hands and the flexor surface of the forearms. The patient may seem and feel well, and yet on close observation this suspicious dermotagra ean often be secn. This is one of the strongest evidences presented by the skin in the periods of intermission and when no other symptom remains of the previous dermatosis.

Another aid afforded by the skin in the periods of intermission is what Sandwith ealls "the preternatural pinkish cleanliness" of the finger tips, and he might have added of the toes also. At times this pink cleanliness ineludes the palmar surface of all the fingers, and it is especially evident when the arms hang down or when the hand of the pellagrin is put by the side of the hand of a healthy person for eomparison. The tips of the fingers seem as clean between the attacks as the back of the hands seem dirty during the attack. This eondition is especially evident in the better class of pellagrins. Along with the abnormal pinkness on the palmar surface is found the inerease in the number of folds or wrinkles over the first interphalangeal joint, and the division of these folds into small areas, which are square, rhomboid, or reetangular in shape, and rather rough. After the attack these folds hang loosely, are increased in number over the usual three to five wrinkles, and, when gently rubbed by the index finger, feel rough. A laborer's hand may have these rough divisions, but the pinkness of the fingers and reduplication of the folds is absent.

Another factor in diagnosis between attacks in regard to eolor is the mosaic mottling of the back of the hands, and a cyanotic condition of the whole hand when the arm hangs loosely by the side. The same condition prevails after the dermatitis on the foot. One can sometimes examine the hand of a pellagrin during the winter months after the attack of the previous spring, and the pink fingers, mosaic mottling and cyanosis, inereased wrinkles and rough areas are of great aid in doubtful cases. I have been able to bring all these symptoms out more elearly by lightly grasping the wrist with my hand and interfering with the circulation. In one case the perspiration burst forth quickly all over the palm of the hand,

and the cleanliness of the pink fingers was wonderful. The hands of the pellagrin can not be too closely studied.

LOCATION.

The location of the dermatosis is influenced by the selective action of the disease, by symmetry, and by light or heat. Merk, with the aid of Weiss, collected pellagra statistics in the south of the Tyrol for the years 1905–1907. These observations included 384,072 inhabitants, of whom 4,836 were pellagrins, or 13.4 per thousand; of these, 2,973, or 61.4 percent, presented some of the cutaneous manifestations of pellagra; and 2,179, or 45 percent of the cases, presented the maculo-papular dermatitis. Of these last the following notations were made:

1,677,	or 77	percent, with dermatitis on the back of both hands.
283,	or 13	percent, with dermatitis on the back of both hands and on the neck.
164,	or 7.5	percent, with dermatitis in rare locations and on the neck.
53,	or 2.4	percent, with dermatitis on other parts of the body.

This table gives ample proof of the selective action of pellagra on the skin. The back of the hands is the most favorite spot, then the neck; in America the feet, face, and then other parts of the body. To the selective action is added the symmetrical distribution, the dermatitis or the dermotagra usually appearing on bilateral areas simultaneously. There are exceptions even to this simultaneous action. Echols at Milledgeville showed me a female pellagrin in his wards on whose right hand the characteristic dermatitis appeared, and after eight days it appeared on the same area on the left hand. Tucker reports the only other case of this kind I have found in the literature. He gives in his 55 collected cases 44 in which the dermatosis began on the back of the hands and forearms; in 7 on the back of the hands, forehead, and alæ of the nose; in 3 on the back of the hands and feet, and in 1 on the back of the hands and neck. The dermatosis remained confined to the hands and forearms in 28; hands, face, and neck in 4; hands, face, feet, and neck in 12. In one case the skin was involved all over the body, the pellagra universalis. In this form the dermatitis is limited usually to the ordinary sites of hands, face, neck, and feet, and the rest of the body covered with the

eczematoid dermotagra. I saw a case of this kind in Italy at Mombello, and one case in Georgia even more remarkable, as there was a dermatitis on the hands and wrists, between the scapulæ, and in the sacral region, extending down in the gluteal folds.

On the hands the dermatitis usually covers the backs, affecting least the terminal phalanges, and it usually extends from two to four inches above the wrist as the pellagrous glove. The eczematoid dermotagra then usually extends above to and including the elbow. At times the dermatitis extends as far as the elbow, or it may skip the elbow and reappear on the arm or under the

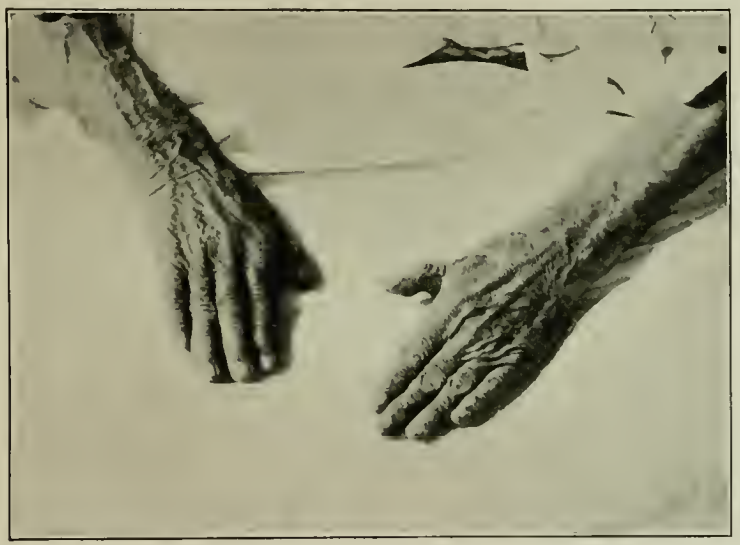


Fig. 24.—An Italian case of senile hands in pellagra. The skin is dry and wrinkled, and lies over the knuckles in folds. (Courtesy of Dr. Bravetta.)

axilla. In advanced or severe cases the dermatitis surrounds the wrist, appearing in triangular form anteriorly as the pellagrous bracelet. The feet, when affected, are covered on the dorsum from the toes to the malleoli, but the dermatitis may extend up the leg for a variable distance, as a rule not above the junction of the lower and middle thirds, forming the pellagrous boot. The knees may be covered, like the elbows, with the keratoid roughness, dirty-brown in color, and the legs may present a mottling anteriorly to the knees.

After the dermatitis departs and the epidermis exfoliates, the

dermotagra persists for a variable period, often permanently. Contrary to Jansen and the Italian writers, it may invade the hand as the keratoid dermotagra. Bravetta had a case at Mombello in Italy. Here the dermotagra invaded the palm from the radial side, advancing under the thumb. This invasion of the palmar surface seems more common in America than in Italy. I have seen several cases where it advanced from the ulnar side, and Zellar in Illinios has seen cases on the soles of the feet, with peeling as in scarlet fever. In negroes the elbows and knees are often covered with persistent ashen-gray roughness, noticeable between attacks.

A discrete dermatitis may occur around the lips, or the pellagrous mask may cover the face with exfoliation. The forehead may be affected with the eczematoid roughness, or mingled with these may be the isolated areas of dermatitis. The dermatitis may stimulate the sebaceous glands and produce a temporary seborrhea. This is more common on and around the nose than elsewhere. A symmetrical dermatitis may appear over the malar bones, below and behind the ears, and crescentic ecchymosis, dermatitis, or dermotagrous spots, always symmetrical, develop on the lower and upper lids. The symmetrical areas of dermatitis may appear on the back of the neck, or a crescentic area cover the back of the neck, concavity upward, and thickest in the median line and extending the same distance on both sides. The dermatitis may surround the neck with a sternal prolongation, which forms the Spanish cravat of Casal. Sandwith has seen this in Egypt, and thinks it due to the open shirt-front of the field laborers. Studying many hundred cases of pellagra, one sees either the dermatitis or the dermotagra in locations rarely described, and which Bravetta well calls "atypical locations." These are in the axilla, on the flexor surface of the elbow-joint, the posterior surface of the knee, on the thighs, the scrotum, a dermotagra making a girdle around the hips, and Dr. Greene at Milledgeville showed me a remarkable case in a young negro with a severe dermatitis entirely around the shoulder, covering an area about four inches wide and making a veritable shoulder girdle of dermatitis, coal black in color. After the attack is over, walnut stain effects are occasionally seen on the face on the order of chloasmic spots. This colored area may persist as a permanent pigmentation without any roughness.

The perineum, vulva, and anal regions in the female are attacked by the dermatitis, occasionally by gangrene, and even a pro-

nounced keratoid condition may be present. In the more serious cases the dermatitis may extend from the inner surface of the thighs upward and backward to the anus and the gluteal region. An acute vaginitis may be present, with a mucopurulent discharge, erosion of the epidermis, and even sloughing of the tissues. The dermatitis may occur on the folds of the labia majora and minora, but the inflammation of the vaginal mucosa is similar in character to the stomatitis. The dermatitis with vesicles is not infrequent when the hands have the same inflammation, and in these cases sloughing and gangrene may develop in the vulvar region a short time before death. J. Clarence Johnson, of Atlanta, had a case in which the vulva and labia majora were covered with a thick, keratoid covering, very rough and dry to the touch. The patient recovered from the attack, and after exfoliation the vulva was normal.

RELATION OF THE DERMATOSIS TO LIGHT.

In the early days of pellagra the sun was believed to cause the disease, and it was called mal de la sol, or sickness of the sun. Jansen remarked that the sun was neither hotter nor different in Italy than in other sections of the world where the disease did not exist, and the dermatitis may occur on parts of the body covered by clothing. In those exposed to direct sunlight the dermatosis in pellagra seems to appear earlier in relation to the other symptoms, and to be synchronous with the diarrhea, whereas in those living indoors the diarrhea or dyspepsia usually precedes the dermatitis. This influence of the sun has been attributed to the shorter or violet rays of the spectrum, known usually as the actinic rays. The work of Aaron would seem to weaken the actinic theory in pellagra, and to cause the belief that the direct heat of the sun was the real influence, with the elevation in temperature of the parts exposed to the sun and of the surface temperature in general as the chief heat factor. Various experiments have been performed with fenestrated gloves. The pellagrous glove itself often extends from four to six inches above the lower border of the sleeves. Bass' ring experiment (Fig. 19) seemed to show protection from the dermatitis when the parts were not exposed to the sun. This much is certain, and proof that the influence of the solar heat is only a very minor influence—a patient must first have pellagra internally be-

fore the sun can cause or influence the dermatitis externally. The disease, and not the sun, causes the pellagrous dermatitis.

The hair is usually not affected in those developing pellagra during adult life, but in children the hair is often short, thick, and coarse, lacks the usual amount of sebaceous matter, and feels rough. It stands up, and does not respond to combing and brushing as

Fig. 25.—Wet form of dermatitis, with sloughing of skin. Unusual lesions in the palms of the hands, due to wringing clothes when washing. The elbows are also affected from pressure when rising from the bed. (Courtesy of Dr. C. C. Bass.)

ordinary hair. In children the hair on the body does not develop normally, but is both scant and short.

The perspiration, normally acid, may in pellagra be neutral. Procopiu found it neutral in 20 cases, acid in 2, and alkaline in 3. In Tucker's 49 cases it was normal in 14, increased in 3, and decreased in 32. In insane pellagrins it has seemed to me that it

was noticeably increased on the feet and hands, and the more advanced the nerve lesions the more variable the amount of sweat. The odor of the body is increased in certain cases, and this is attributed to the fetid sweat. The sebaceous glands of the skin are at times overactive—more pronounced, as is to be expected in young pellagrins.

The nails are occasionally affected. They turn white or grayish

Fig. 26.—Rough hands of a pellagrin as contrasted with the normal hand of a hospital orderly. (Courtesy of Dr. Bravetta.)

white, are thick, and in the spatulate hand are very wide and brittle. This is a rare occurrence, and occurs usually in advanced cases—especially in the insane and following a hemiplegia in old pellagrins. Here it is probably trophic in nature and dependent on the pellagrous process in the nervous system. It is found in the asylums for the insane rather than in pellagrins in private practice. Occasionally the nails fail to receive sufficient nourishment from the blood and actually drop off. Such trophic changes rarely occur in private practice.

SENSORY SYMPTOMS.

The sensory symptoms in ordinary cases consist of either tenseness or tightness of the skin over the dermatitis areas and in those with vesicles, bullæ, and swelling; itching sensations; and, lastly, the most constant and irritating of the three is the burning of the hands and feet, and infrequently other parts. For a few days before the eruption the skin may feel tense and tight as if it were

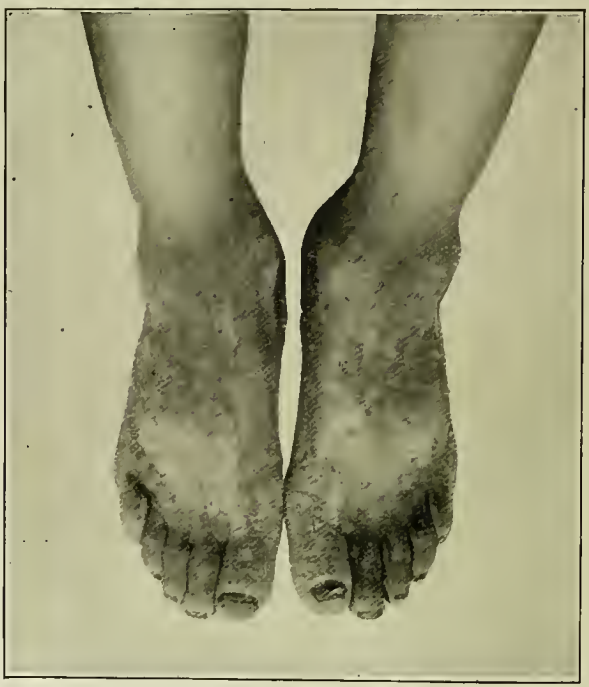


Fig. 27.—An Italian case of typical dermatitis, showing the feet during an attack. (Courtesy of Dr. Bravetta.)

being stretched or the hand and forearm were swelling. This is of short duration, reaches its maximum at the height of the dermatitis, and recedes rapidly with the exfoliation. In the dermatitis with vesicles—the wet form—the swelling and tenseness may be increased even to a condition of edema in the inflamed parts, with the hands swollen and heavy. After rupture of the bullæ, this tightness of the tissues and edema rapidly ceases.

The itching is a minor symptom, and patients complain of it

very little. Sandwith, in his 164 cases, had itching in 71, burning in 3, and in 90 neither symptom was present. In the American cases the percent of burning would certainly rank much higher, and the patients complaining of itching much less. Indeed, one seldom notes itching sufficient to cause scratching to any degree. Whatever actual pruritus exists is apt to be heightened by burning sensations, and it is the heat rather than the itching that causes the discomfort. The burning may occur on the back between the scapulæ, over the sacrum or coccyx, and it may be intense around the anus and in the perineal region. It may cause insomnia, and

Fig. 28.—Pellagrous dermatitis. Hand swollen and edematous. (Courtesy of Dr. Bravetta.)

the patient complains that if the burning would only stop he could sleep without trouble. Warnock thinks there is a connection in the pellagrous insane between the sensations of burning and the well-known complaint of discomfort and delusions of being burnt, of sorcery, and of persecution. The area of burning may become red in the periods of intermission, and in the advanced cases the burning often continues long after the attack has receded. This burning is probably central in origin along with the burning felt in the stomach at the height of the attack. In the advanced neurasthenic stage, with mental failure, the burning causes a de-

sire for cooling and for water, and many of the suicides by drowning formerly common in the Tyrol can be explained in this way. One of my cases had no itching or burning, but developed the most

Fig. 29.—A Georgia case, showing exfoliation of the skin following a spring attack. Period of recession. (Courtesy of Dr. J. O. Elrod, Forsyth, Ga.)

persistently cold nose I have ever seen. It was cold to the touch, and the patient said the tip seemed changed to a small piece of ice.

CHANGES IN THE SKIN.

The subcutaneous fat and areolar tissues disappear in proportion to the severity and the length of the disease. In any case with a marked dermatitis there is an atrophy of the skin, with wrinkling and often even folds, so that one is struck with the youth of the pellagrin and the senility of the skin. The hands are those of old people, and the face may look old as a result of the wrinkling and puckering of the brow. By pulling up the skin on the back of

Fig. 30.—An Italian case of alcoholic erythema, due to alcohol and not to pellagra. (Courtesy of Dr. Bravetta.)

Fig. 31.—An Italian case of alcoholic erythema, due to alcohol and not to pellagra, and of the same character as Fig. 26. (Courtesy of Dr. Bravetta.)

the hand, it is loose and there seems too much of it—a condition that Italians call "pelle elastica." After two or more attacks of dermatitis the skin is permanently atrophied, and the site of the inflammation is covered with a thinned, cicatriform, parchment-like integument—this last being often irregularly altered—and the thinning showing occasionally in stripes parallel with the long axis of the hand. (Hyde.) The skin becomes permanently pigmented and discolored, and there may be a universal bronzing. The eczematoid dermotagra may become permanent in the dermatitis

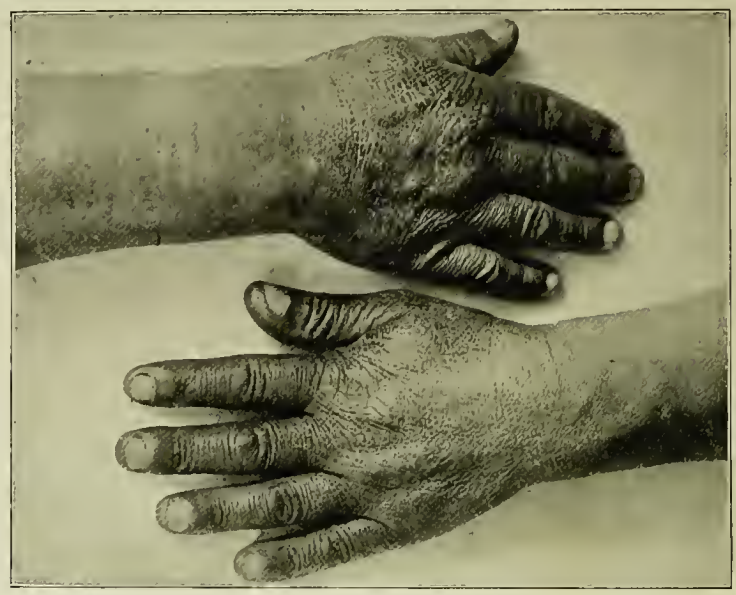


Fig. 32.—A close view of the rough skin in pellagra, showing areas of exfoliation. Hand swollen and edematous. (Courtesy of Dr. Bravetta.)

area as well as in the original site of the roughness on the forearm, elbow, and face.

The microscopical changes are like those of a mild acute inflammatory condition, with a degeneration of the upper layers of the dermis. The skin in the beginning of the dermatitis is hyperemic, with an exudate of serum and leukocytes, and with no change in the superficial and terminal nerves. (Harris.) Following the degeneration with the involvement of the connective tissue around the blood vessels, repair begins with an increased cellularity of the dermis, the presence of fibroblasts, pigmentation, eczematoid

sealing and shedding, and with an increase in the lymphocytes and plasma cells. The sweat and sebaceous glands are hypertrophied and enlarged. There is an increase in the number of capillaries, with a corresponding increase in the thickness of the skin in the prickle cells and stratum granulosum. In ulceration the epidermis is absent, and there is loss of substance in the upper part of the

Fig. 33.—Pellagrous dermatitis. Hand swollen and edematous. (Courtesy of Dr. Bravetta.)

dermis. As atrophy continues, the epithelium dips deeply into the thinned connective tissue. Gurd believes the irritant is in the dermis, with the addition of some predisposing factor. There is an enormous increase in the formation of pigment in the cells, and an increase in the number of chromatophores in the upper dermal layers. The pigmentation originates in both types of cells, and, so far as is known, remains where it originates.

CHAPTER VI.

NERVOUS SYSTEM IN PELLAGRA.

The pellagrin is the warehouse of all the symptoms of neurasthenia. The very name and presence of the disease causes him to fear and to forebode. The dermatosis gives him a sense of filth and repugnance; the gastrointestinal condition reacts on him both mentally and physically; and added to these are the deeper tissue changes in the cerebrospinal axis, which constitute the organic basis for what is at first a neurasthenia, and which later is the worn-out soil in which spring up tremors, pains, increased reflexes, palsies, paretic and spastic gaits, trophic changes, mental retardation, and finally psychoses of different types, inanition, and death. The pathological changes in the nervous system are definite in varying limits, and their study clears the clinical nerve symptoms of much uncertainty. Like the course of pellagra, these changes in the nervous system are slowly progressive in the chronic forms and rapidly progressive in the acute forms. Progression applies as well to the tissue changes as to the external clinical symptoms.

TISSUE CHANGES.

The Brain.

Gross Changes.—The pia mater and arachnoid are thickened with occasional thickenings of the dura. The piarachnoid may be opaque and milky, with purulent deposits under the arachnoid or hemorrhagic ecchymosis. Osseous plaques may be formed and a typical lepto-meningitis exist. The brain and its convolutions, especially the frontal, show atrophy, and the weight of the brain is decreased in the majority of cases. The brain may be partially or completely edematous or hyperemic, with excess of fluid in the ventricles. It may be anemic, and harder on one side than the other. The cerebellum is either small and hard, or edematous and soft. These gross changes are variable, as shown by the fact that the brain may be either increased or decreased in weight. War-

nock found the brain weight 1,300 grams, with body weight of 46 kilograms, in an old pellagrin 45 years old, who was "passive, prostrate, and demented."

Microscopical Changes.—The capillaries show pigmentation and fatty degeneration in their walls, and occasional calcareous deposits. The small arterioles and capillaries are filled with blood and the perivascular lymph spaces dilated. This condition explains the increased fluid found in the ventricles in certain cases. The cortical nerve cells show degeneration, with swelling, vacuoles form, the nuclei and nucleoli are swollen and pushed to one side.

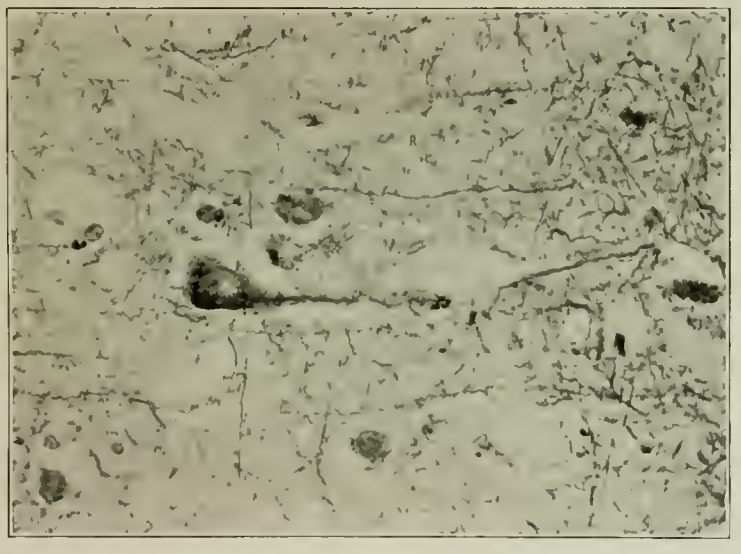


Fig. 34.—Cortical cells. Pigmentary degeneration. Method of Cajal. (By Dr. Bravetta.)

The granules disintegrate in advanced cases, and the dendrites swell and break. The neuroglia cells, especially around the vessels, swell, and Babes and Sion found small collections of lymphoid cells, but this latter was not confirmed by Harris. There is atrophy of the degenerating cells and also degeneration of the fibrillar structure in the cell body. Harris studied the cells of the cerebellum and noted degeneration, atrophy, and at times disappearance of many of the cells of Purkinje. In one instance he found the molecular and granular layers separated by microscopic spaces that probably existed during life.

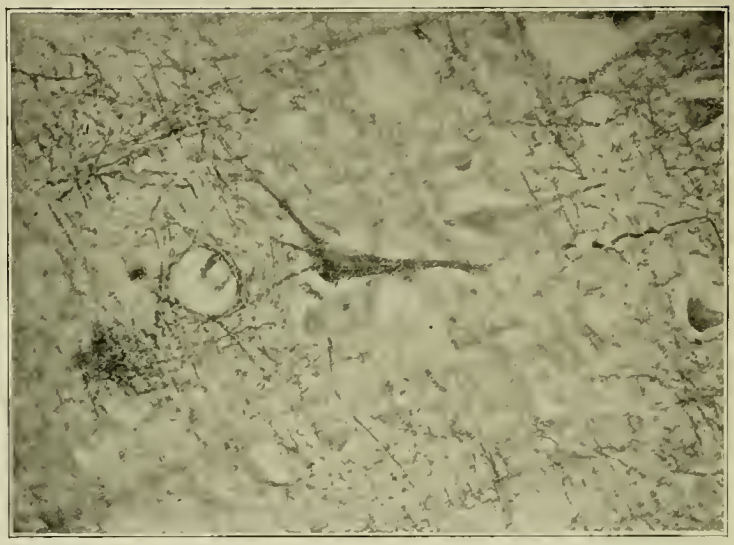


Fig. 35.—Cortical cell, showing contraction of the protoplasm. Method of Cajal. (By Dr. Bravetta.)

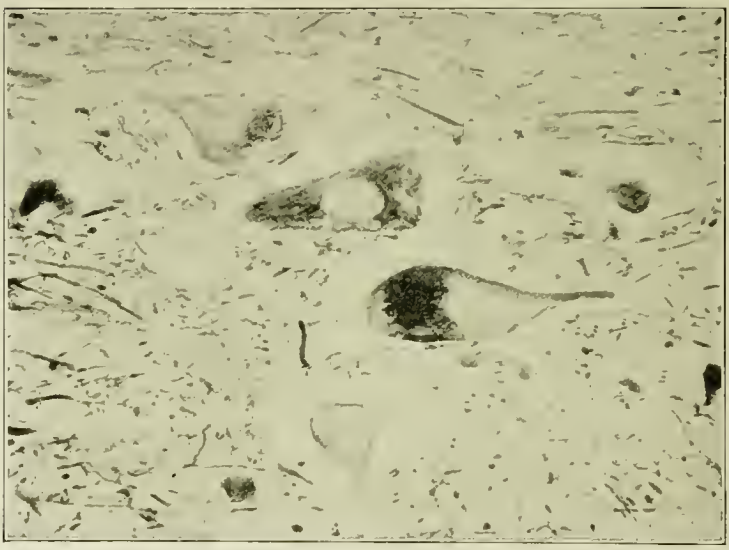


Fig. 36.—Cells from the spinal cord, showing thickening and contraction of the neurofibrillar net, or special net of Marinesco. Method of Cajal. (By Dr. Bravetta.)

The Cord.

Gross Changes.—These gross changes are not as evident in the cord as in the brain. In acute pellagra an acute meningo-myelitis may be present, with inflammation of the meninges and a superficial edema and softening. The superficial vessels are dilated.

Microscopical Changes.—These changes include chiefly degeneration in the direct pyramidal tract and in the posterior column, including both the tracts of Goll and Burdach. The gray matter

Fig. 37.—Cells from the spinal cord, showing partial thickening and contraction of the neuro-fibrils. Method of Cajal. (By Dr. Bravetta.)

and the spinal ganglia are affected to a degree. A tabular summary follows:

1. *Tracts.*—The tracts of Goll and Burdach show degeneration and a profuse proliferation. These tracts are pale compared with the rest of the cord. Occasionally degenerate roots entering in lumbar region can be traced up into the dorsal region. There may be degeneration of the posterior roots and an increase in the connective tissue around these roots, with occasional thickening of the arteries. The degenerate areas in stained preparations show like small spots of ink spattered all over the posterior column.

2. *Direct Pyramidal Tract.*—There is more or less degeneration

and scattered areas from which the nerve fibers have disappeared. Occasionally swollen axis cylinders are found. (Spiller.)

3. *Gray Matter.*—There is pigmentation of the cells of the anterior and posterior horns. The recticulum of many of the cells is clearly evident, and the fibrils appear contracted and the cell smaller. The degeneration in the cells of the posterior horns appear degenerated from the cervical region downward, and especially are the cells in Clarke's column affected. Spiller found cells in the anterior horn in the lumbar region degenerate, the cell body swollen, the nucleus displaced to the periphery, dendrites gone, and

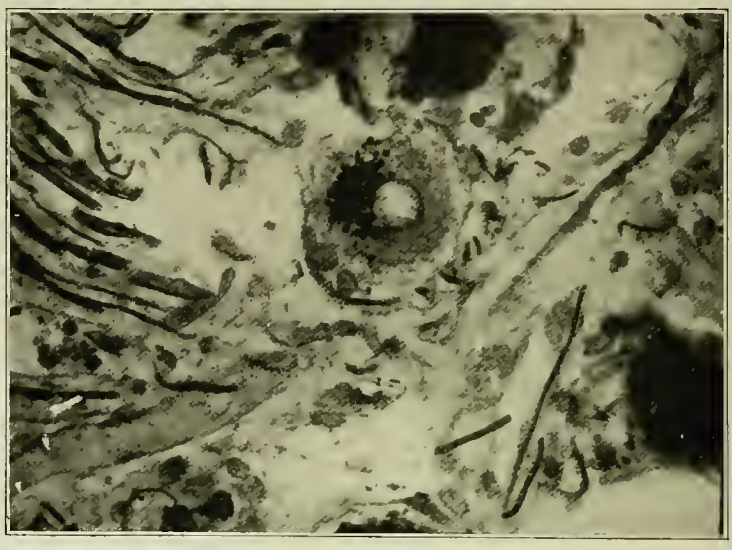


Fig. 38.—Cell from spinal ganglion. Pigmentary degeneration. Method of Cajal. (By Dr. Bravetta.)

intense chromatolysis. Bravetta, of Mombello, showed me slides with an increase in the neuroglia elements, and others with sclerosed and isolated masses of gray matter, indicating the chronic nature of the process in the cord. Bravetta showed pigmentation and degeneration in cells in the spinal ganglion. Spiller found the capsules of the cells in the ganglia in the lumbar region showed much proliferation of the lining cells, and, like Bravetta, the nerve cells presented a marked degeneration. The Nissl granules also disappear in some of the cells of the medulla, and there occurs in such cells a yellow pigmentation. (Bravetta.) Pigmentation,

swelling of the body of the cell, disappearance of the dendrites, chromatolysis, and displacement of the nucleus peripherally summarize the changes in the gray matter.

Dejerine reported a case with degeneration in the nerves on the back of the hand, but the patient was a chronic alcoholic instead of a pellagrin. In general, it may be stated that the peripheral nerves are normal. Bravetta in all his researches found the nerve fibers

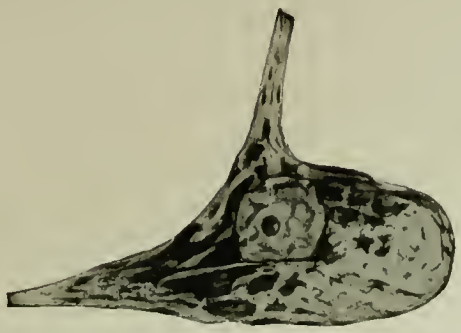


Fig. 39.—Chromatolysis and pigmentary degeneration in cells of the cord. Method of Nissl. (By Dr. Bravetta.)

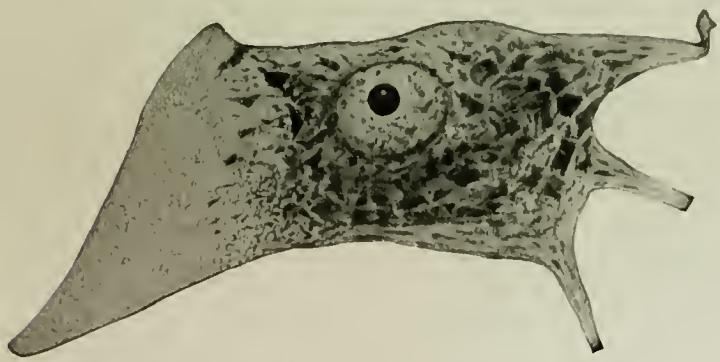


Fig. 40.—Same case as shown in Fig. 39. Chromatolysis and pigmentary degeneration in cells of the cord. Method of Nissl. (By Dr. Bravetta.)

intact. Spiller studied the sciatic nerve and found the nerve fibers normal, but the connective tissue of the nerve and the intima of the vessels were proliferated. Whatever sensory changes exist in pellagra find their cause in the spinal ganglia and the cord, and not in the nerves, as in an ordinary neuritis. The process in the cord is chronic. The Marchi method often shows in the posterior column sclerosis, but no degeneration. Six out of eight of Tuc-

zek's cases showed the sclerosis chiefly in the dorsal region, and this may account for the pain in the back so often complained of by pellagrins. The chief anatomical lesions in the cord are the degenerations in the posterior column and in the direct pyramidal

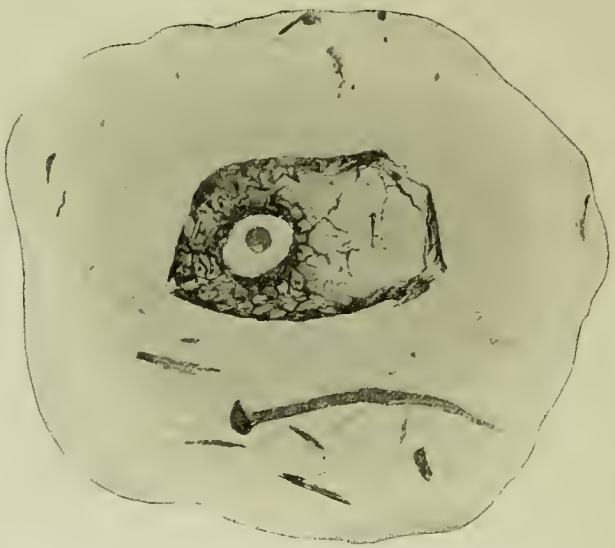


Fig. 41.—Cells from the cord, showing yellow pigmentation and degeneration. Method of Donaggio. (By Dr. Bravetta.)

Fig. 42.—Same case as shown in Fig. 41. Cells from the cord, showing yellow pigmentation and degeneration. Method of Donaggio. (By Dr. Bravetta.)

tract in the lateral column. This distribution of degenerative changes resembles ataxic paraplegia, but in the latter the cellular changes in the horns and the meningo-myelitis is absent.

The tissue changes in the cord are important, viewed both from their relation to clinical symptoms and to the ultimate cause of

pellagra. Mayr in Hebra's work says: "The science of pathological anatomy has as yet contributed nothing toward the explanation of this mysterious malady." Spiller has commented on this point more fully than any other authority in nerve pathology, and it is well to note carefully his conclusions.

"It is evident from the brief abstracts of the foreign representative papers treating of the pathology of pellagra that there

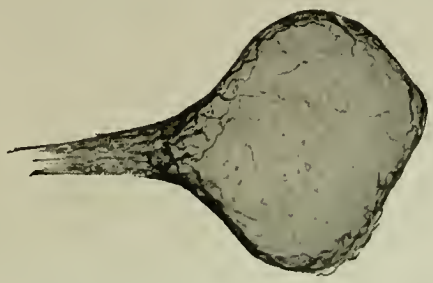


Fig. 43.—Spinal cord. The cellular body is entirely invaded by yellow globular pigment, and passed through by few thin fibrils, which form a net. Neuro-fibrillar method by Donaggio. (By Dr. Bravetta.)

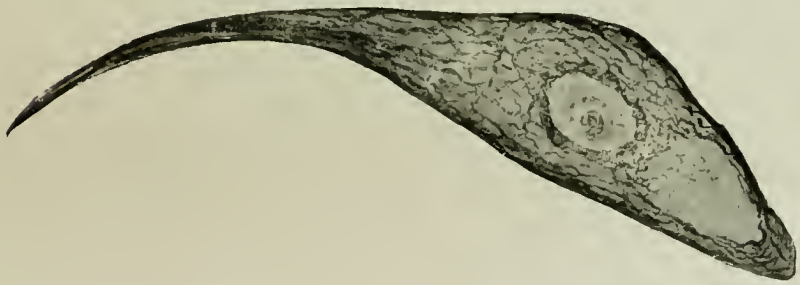


Fig. 44.—Spinal cord. The cell is partially invaded by yellow globular pigment. Degeneration of the nucleolus, perinuclear membrane, and long fibrils. Neuro-fibrillar method by Donaggio. (By Dr. Bravetta.)

is a difference of opinion in regard to the systemic or nonsystemic appearance of the degeneration in the spinal cord. This is a matter of some importance, as a toxic degeneration is more likely to be nonsystemic. In the two cases I have studied the degeneration was diffuse. Indeed, from my own experience I have come to believe that, with the exception of Friedrich's ataxia, there are few disorders causing a truly combined systemic disease of the spinal cord. The degeneration observed in anemia is not systemic, but

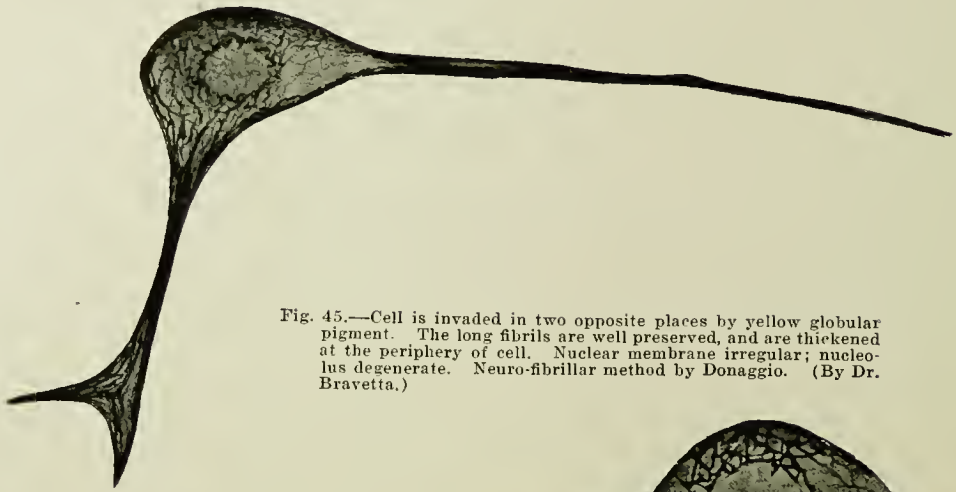


Fig. 45.—Cell is invaded in two opposite places by yellow globular pigment. The long fibrils are well preserved, and are thickened at the periphery of cell. Nuclear membrane irregular; nucleolus degenerate. Neuro-fibrillar method by Donaggio. (By Dr. Bravetta.)

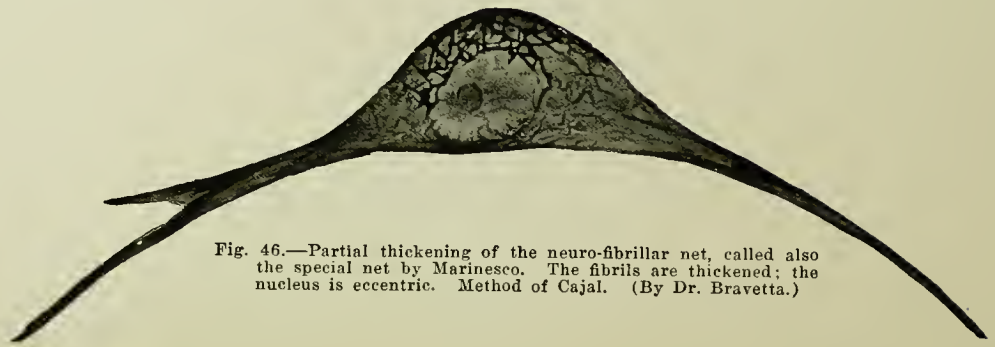


Fig. 46.—Partial thickening of the neuro-fibrillar net, called also the special net by Marinesco. The fibrils are thickened; the nucleus is eccentric. Method of Cajal. (By Dr. Bravetta.)

in the cases I have studied (quite a large number) it has invariably been a diffuse process. It is more intense than I have observed in pellagra, but **not of an essentially different character.** The nerve cells, however, are much more affected in pellagra than in anemia.

"Writers seem to agree as to the pronounced degenerative changes in the cells of the anterior horns of the spinal cord and of the cortex of the cerebral hemispheres in pellagra. It appears from the first case reported in our paper that the moderate degeneration of the pyramidal tracts predominate clinically over the apparently more intense alteration of the cells of the anterior horns, so that exaggeration of the patellar reflexes was present.

Fig. 47.—Spinal cord. Pigmentary granular degeneration. Method of Cajal. (By Dr. Bravetta.)

"The view has been expressed (Long) that the thickening of bone about the intervertebral foramina, possibly more in the cervical region, may be a cause of the symptoms. Unfortunately, only the extreme lower part of the cord in the cervical region in case 1 was obtained, but posterior and anterior roots from this region, cut separately, show no distinct degeneration, even by the Marchi stain. Had these roots been implicated in the intervertebral thickening, degeneration would have been detected in them. I have found no indication of root degeneration in the thoracic or lumbo-sacral region, and the alteration of the posterior columns, at least below the eighth cervical segment, is clearly endogenous, as it is also in the piece of thoracic cord obtained in the second case.

"I must conclude, so far as a study of these two cases permits, that pellagra does not always produce—if, indeed, it ever does produce—a truly systemic disease of the central nervous system, but that the degeneration is caused by some toxic or infectious substance affecting all parts of the cerebrospinal axis, producing cellular degeneration and diffuse degeneration of nerve fibers in

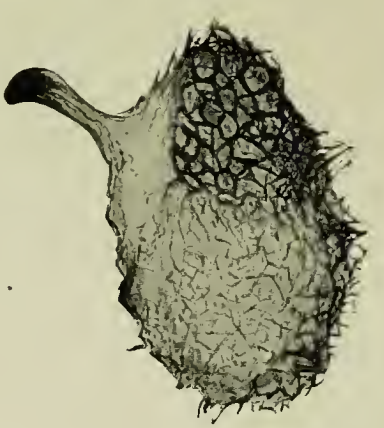


Fig. 48.—Spinal ganglia; outlines irregular. Invasion of the special net or Marinesco's net. Method of Cajal. (By Dr. Bravetta.)

the posterior and antero-lateral columns. It is not difficult to explain the mental symptoms when cortical degeneration is so intense as may occur in pellagra, and as is seen in the brain I have studied; and the insanity in this disease seems to be of a toxic or infectious character."

RELATION OF CORD LESIONS AND CLINICAL SYMPTOMS.

The most striking summary of these changes is given in Hyde's article on Dr. Bassoe's work. I have used this classification as a working basis in pellagra cases, and find it admirable. There are three types of cord lesions, considered clinically and related to the cord tracts chiefly affected. I give Hyde's account:

(a) **Probable Pyramidal Tract Degeneration—Case 1.**—Demented male epileptic, aged 37 years, admitted April, 1902, previously at a poor farm and another state hospital. Insane for nineteen years. Diarrhea and erythema of the hands during the past summer. The hospital record mentions increased tendon reflexes and positive Babinski sign on August 31, 1909. Examination on October 10th revealed increase of all tendon reflexes without

clonus; inconstant Babinski and Oppenheim signs; pupils react to light. There is a slight swaying in Romberg's position, but the patient walks well and the heel-knee test is as good as can be expected in a demented subject. A note was made on October 31st that he had had stomatitis and diarrhea for several weeks, and lost forty pounds in weight.

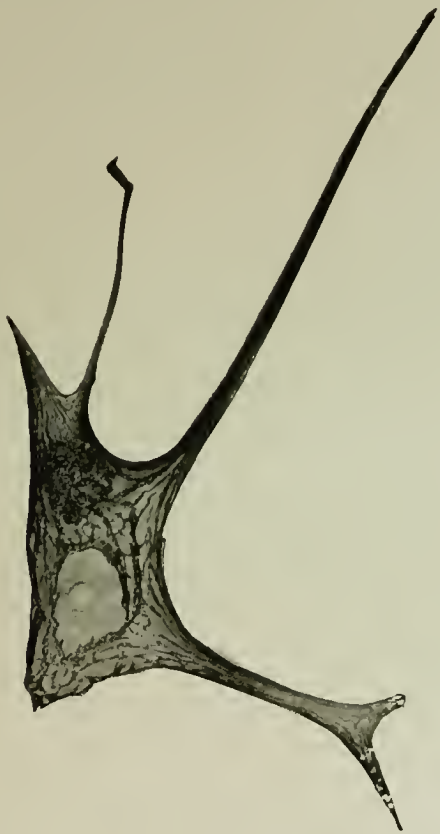


Fig. 49.—Spinal cord. Thickening and concentration of the neuro-fibrillar net. Nucleolus enlarged and irregular. Method of Cajal. (By Dr. Bravetta.)

(b) **Posterior Column Degeneration—Case 2.**—An elderly demented woman developed characteristic skin lesions in August, 1909. Ataxia is so marked that she can not walk or stand alone. The wrist, elbow, knee, and ankle reflexes are lost. No Babinski sign. No involuntaries. Pupils normal. Characteristic erythema of the hands and face when examined on October 10th.

(c) **Combined Degeneration—Case 3.**—A woman, aged 50 years, was admitted in November, 1908, with a history of having been insane for fourteen months. On admission she was fairly well nourished and the tendon reflexes

were normal. The psychosis was melancholia of involution. On August 27th the wrist and elbow reflexes were recorded as normal; the knee reflexes as increased. No Babinski sign at that time. On October 10th she was emaciated, with severe stomatitis and diarrhea. The wrist jerks and the left elbow jerks were absent; the right elbow jerk, weak. Knee and ankle jerks absent. Inconstant Babinski sign on the right side; normal flexor response on the left side. The pupils react rather sluggishly to light. She died on the following day. No necropsy. It seems probable that the pyramidal tracts were first involved, causing increased knee reflexes. Later, the posterior columns degenerated sufficiently to abolish nearly all of the tendon reflexes.

Sympathetic Nervous System.

The study of the sympathetic system has been done by R. Brugia, of Bologna, and summarized by Antoniui.

1. In all insane pellagrins the sympathetic nervous system is injured and the changes are extensive in all its component parts.

2. The ganglia of the cervical region and the abdomen are affected differently, according to the extent of the common forms of the pellagrous psychoses or of acute pellagra.

3. In the prevailing forms there is hyperplasia of the connective tissue, with sclerosis, a constriction of the vessels, a reduction in the number of nerve cells with atrophy, and a pigmentation plainly visible; in these at times there is a form of hypertrophic degeneration.

4. In the acute relightings of the pellagrous process the particular elements present entirely different appearances. Only rarely is atrophy seen. Instead there occurs a turbid swelling of the cytoplasm, a central and peripheral chromatolysis, complete absence of the chromatic granules, and a variety of lesions in the nucleus and the nucleolus; in the supporting tissues a diffuse infiltration with leukocytes, a proliferation of endothelium and the formation of capillaries, circumscribed hemorrhages, points, and areas of softening.

5. In every case, and more particularly in the chronic forms, the lesions are greater in the abdominal ganglia, both centrally and cortically.

6. With the degeneration of the abdominal sympathetic there occurs acetonuria and the paretic diarrhea so frequent in insane pellagrins; while the lesions of the cervical sympathetic contribute in great part to cause the characteristic erythema, with the habitual dryness of the skin and the changes in the pupils.

The conclusions in the last paragraph require further investigation for their confirmation. The extent of the part played by the sympathetic system in pellagra is not yet determined.

CEREBROSPINAL FLUID.

I am indebted to Dr. S. S. Hindman, pathologist to the Georgia State Asylum, for permission to use the results of his work on the spinal fluid in pellagrins. These patients came from the wards

of Dr. W. J. Cranston, who did all the punctures, and the work was done under the direction of Dr. E. M. Green, clinical director. The table on page 156 shows the results of these counts in detail and the averages at the foot of each column. Chemically the fluid is acid in reaction, twenty-three of the twenty-five cases are positive to the butyric acid test, and all of the twenty-four specimens tested

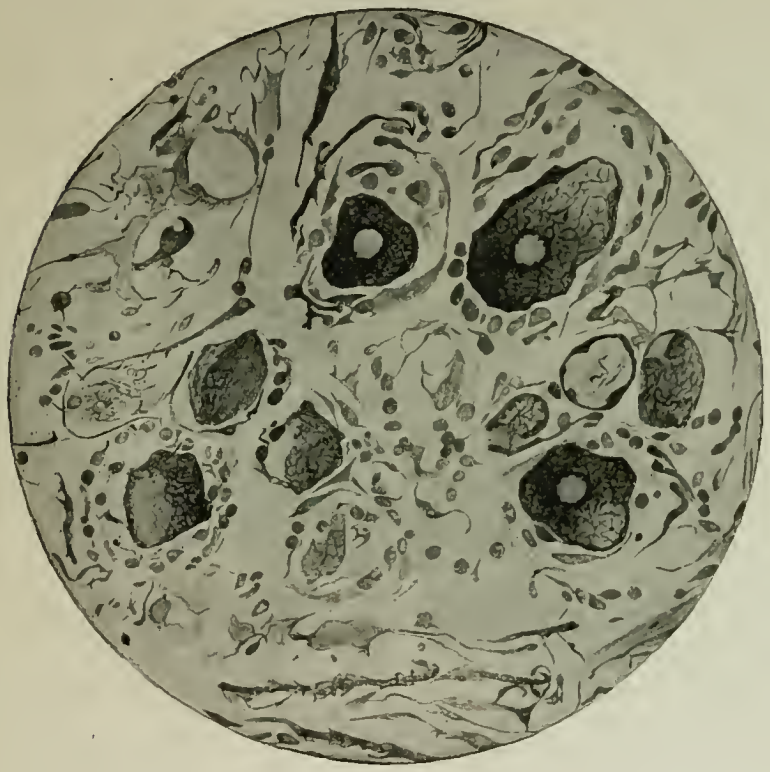


Fig. 50.—Spinal ganglia. Changes in the fibrillar net; changes in the nucleus. One may see the different phases of degeneration in the cell. Only one cell normal. Neurofibrillar method of Donaggio. (By Dr. Bravetta.)

reduce the copper sulphate solution. The average number of cells to the cubic millimeter is 35, and the percent of the cells in a differential count follows.

In four cases taken in the intermission period between attacks Hindman found the total cell counts at 30, 17.7, 6.6, and 4. This is quite a decrease as compared with an average count of 35 during the outbreak of the attack. Further, in two of these four cases

EXAMINATION OF CEREBROSPINAL FLUID—MICROSCOPICAL AND CHEMICAL.

No.	Reaction	Butyric acid test	Reduces $CuSo_4$	Total cell count	Small lymphocytes	Polymorphonuclear cells	Endothelial cells	Plasma cells	Unknown	Large lymphocytes
1	Alkaline	Positive	Positive	24.4	43.4	21.7	8.6	8.6	17.3	.....
2	Alkaline	Positive	Positive	21.1	42.1	31.5	10.5	.....	15.7	.....
3	Alkaline	Positive	.....	15.	Many	.....	Few	.....	.....	Few
4	Alkaline	Positive	Positive	24.	.....	.....	.....	.....	.....	.....
5	Alkaline	Positive	Positive	55.5	46.	24.	16.	8.	6.	.....
6	Alkaline	Positive	Positive	24.4	27.2	31.8	20.7	9.9	9.9	.....
7	Alkaline	Positive	Positive	72.2	53.8	23.	15.3	.....	7.5	.....
8	Alkaline	Positive	Positive	24.4	21.7	21.7	42.	.....	13.	.....
9	Alkaline	.....	Positive	4.	Few	Few	.....	.....	.....	.....
10	Alkaline	Positive	Positive	40.	Few	.....	Few	.....	.....	.....
11	Alkaline	Positive	Positive	2.	Few	.....	.....	.....	.....	.....
12	Alkaline	Positive	Positive	22.2	40.	30.	10.	.....	20.	.....
13	Alkaline	Positive	Positive	13.3	33.3	25.	6.6	8.3	16.6	.....
14	Alkaline	Positive	Positive	20.	27.7	22.2	27.7	.....	22.2	.....
15	Alkaline	.....	Positive	7.	2.	.....	Few	.....	.....	.....
16	Alkaline	Positive	Positive	42.2	34.2	23.6	18.4	10.5	13.1	.....
17	Alkaline	Positive	Positive	16.3	18.4	12.2	12.2	3.	51.5	1.8
18	Alkaline	Positive	Positive	55.	41.8	18.1	9.	7.2	23.6	.....
19	Alkaline	Positive	Positive	55.5	46.	10.	18.	4.	22.	.....
20	Alkaline	Positive	Positive	64.4	51.1	13.7	12.	6.8	15.4	.....
21	Alkaline	Positive	Positive	33.3	26.6	13.3	40.	3.3	16.6	.....
22	Alkaline	Positive	Positive	38.8	20.	11.4	31.4	5.7	22.8	8.5
23	Alkaline	Positive	Positive	17.7	45.5	8.2	24.3	8.5	13.3	.....
24	Alkaline	Positive	Positive	36.6	54.2	5.	23.6	7.5	9.5	.....
25	Alkaline	Positive	Positive	30.	52.7	8.2	20.1	8.1	10.1	.....
Average No. cases	All alkaline	23 positive 2 negative	24 positive 1 not tested	Average 35; 25 cases	Average 36.3; 20 cases	Average 18.6; 19 cases	Average 19.2; 19 cases	Average 7; 14 cases	Average 17; 19 cases	Average 5.1; 2 cases

the butyric acid test was only very weakly positive, and in the other two it was actually negative.

Comparing Hindman's table with the results obtained in other diseases, excess of lymphocytes is present in syphilitic meningitis and syphilitic disease of the nervous system, in tabes and general paresis. Purves Stewart found in fifteen tabetics the average count

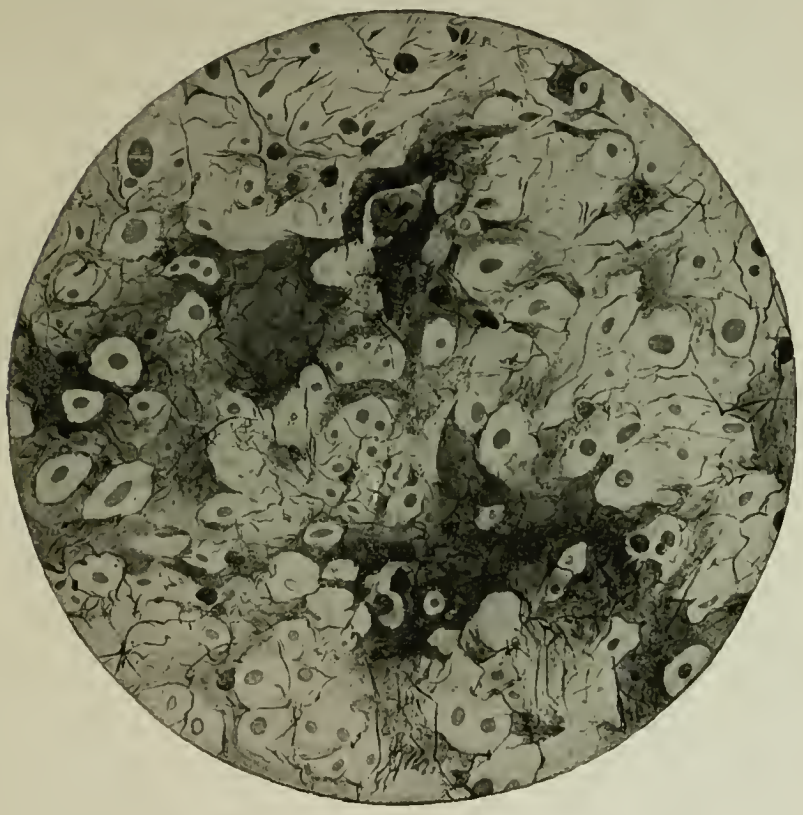


Fig. 51.—Spinal cord. Increase in the neuroglia in crossed pyramidal tract. Weigert's method. (By Dr. Bravetta.)

per cubic centimeter was 125 cells. In tabes and general paresis the spinal fluid often reacts positively to the butyric acid test. In meningitis there is an excess of the polynuclear cells, except in the later stages, when the lymphocytes may be increased as compared with the early stages. In a case of syphilitic meningitis reported by Batten in Allbutt's System the lymphocyte count was 92

percent. In tubercular meningitis there is often a lymphocytosis. The spinal fluid in pellagra is evidence that the pellagrous process includes in its advance organic changes in the nervous system, and that in general these changes are part of a chronic disease, as evidenced by the association of the lymphocytes, whereas acute organic diseases of the nervous system are associated with an increase in the polynuclear elements. In pellagra the lymphocytes are increased both in the blood and in the cerebrospinal fluid.

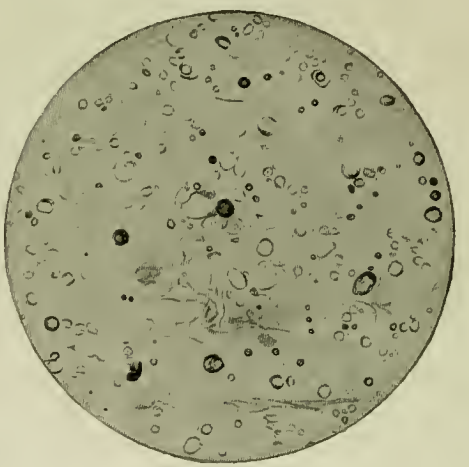


Fig. 52.—Spinal cord. Section of Burdach's tract, showing several fibers and primary degeneration. Method of Donaggio. (By Dr. Bravetta.)

This condition in pellagra is so important in view of further researches that I give in full Dr. Hindman's description of his technic and references, which may be of service to other workers.

Examination of Cerebrospinal Fluid—Microscopical and Chemical.

By Dr. S. S. Hindman, Georgia State Asylum.

Technic used was similar to that of Fuchs and Rosenthal and as modified by other workers.[1]

The first 4 or 5 cubic centimeters of fluid are collected in a sharp-pointed centrifuge tube, and subsequently used for drop or smear method in making differential count.

[1] Bybee and Lorenz: Report of Fifty Examinations of Cerebrospinal Fluid, with Special Reference to the Cell Count, Archives of Internal Medicine, January, 1911; Bulletins Nos. 1, 2, 3, Government Hospital for Insane, Washington, D. C., 1909, 1910, 1911; F. J. Farnell: "The Cerebrospinal Fluid and Its Cellular Elements and Globulin Content." American Journal Insanity, vol. 68, No. 1, July, 1911; J. V. May (1911): Report of Binghamton State Hospital, New York.

The second 1 or 2 cubic centimeters are collected in a small test tube, and used as soon as possible for chamber method for total cell count per cubic millimeter. To that part collected in a small test tube was added 1 or 2 drops (from capillary pipette) of Fuchs-Rosenthal stain, which consists of

Methyl violet	0.1
Glacial acetic acid	2.0
Distilled water	50.0

Filter and use.

The tube is shaken thoroughly and allowed to stand for five or ten minutes in order to stain all of the cells present (red cells, if present, do not take the stain in such short time). A few drops are withdrawn from the tube

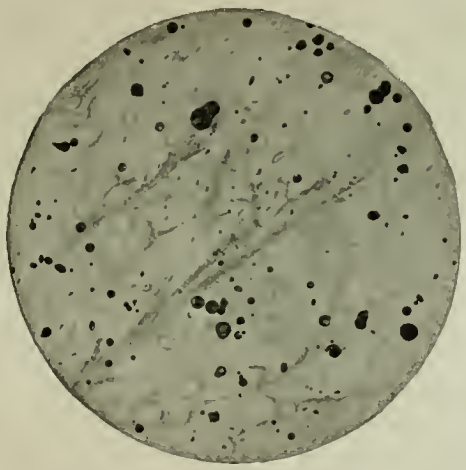


Fig. 53.—Spinal cord. Section of Burdach's tract, showing numerous fibers in secondary degeneration. Marchi's method. (By Dr. Bravetta.)

by means of a freshly made capillary pipette, and, after allowing 2 or 3 drops to escape, 1 drop is placed in the counting chamber of a hemaeytometer (Zappert's ruling), cover glass adjusted, and slide is allowed to stand on the stage of the microscope for at least fifteen minutes before counting to allow all cells to settle upon ruled surface.

The number of cells in the entire ruled surface of nine large squares are counted. Divide the result by nine for average of one, and multiply by ten (one-tenth required depth in one layer), and you have the number of cells per cubic millimeter. As the addition of 1 or 2 drops of stain to 2 cubic centimeters of fluid reduces the dilution to a minimum, it is not necessary to use the white cell pipette as recommended by many workers. In fact, some authorities, in using the pipette, by drawing in 1 part stain to 100 parts of fluid and shaking, etc., have entirely disregarded the dilution in their calculation. One drop of stain from a capillary pipette added to 3 cubic centi-

meters of fluid and shaken thoroughly will stain all lymphocytes and other elements sufficiently well for the count, and give practically no appreciable error. The important point to observe is to make the count as soon after puncture as possible, owing to the tendency of the cells to settle to the bottom.

As to the degeneration of cells on standing, this in our experience does not occur nearly so quickly as some have stated. A larger counting chamber, with a larger ruled surface and greater depth, has been used extensively by others, which is necessarily more accurate for cases showing only a slight increase in cellular elements. In these cases here reported at least two separate counts were made in each case and an average taken for final result.

That part of fluid collected in centrifuge tubes was swung at the rate of 2,500 or 3,000 revolutions per minute for thirty minutes in an electrically driven centrifuge; supernatant fluid poured off and tubes allowed to thoroughly drain; sediment is then taken up with freshly made hair pipette and deposited in not less than 2 drops on newly cleaned slide, spreading out sediment so it will cover approximately a surface one-half centimeter in diameter. Smears are allowed to dry in the air, fixed with absolute methyl alcohol for one to two minutes, and stained with Delafield's hematoxylin and eosin, allowing three to five minutes for former and one to two minutes for the eosin. Any excess of stain can readily be removed by passing through 95 percent alcohol, etc., as staining tissues.

The slides are examined under an oil immersion lens, and a rough differentiation of cells made from counting at least 300 cells.

Lymphocytes are generally in excess and are easily seen, and appear as small dark cells (or nuclei, with little or no protoplasm), varying in size from a little less to a little larger than the size of a red blood cell. For more complete description see Bybee-Lorenz and other references mentioned above. This type of cell is generally agreed upon and can not be easily mistaken for any other.

Polymorphonuclear elements present considerable variation in their characteristics, and some are not very definite; for the most part, they resemble more or less the same type found in the blood, but show different divisions of nuclei, and are usually smaller and stain differently. "The protoplasm of the larger cells usually is very faintly pink, while the smaller types stain a deeper rose color." (Bybee and Lorenz in their original article.)

Plasma cells, as described by Bybee and Lorenz, vary in size from a little less than a red cell to two and rarely three times their size. Nucleus is darkly staining, but does not approach the inky blackness of the small lymphocyte. (For complete description see original article of Bybee and Lorenz.)

Endothelial cells in these cases include all of that variety, but it should be mentioned that the ordinary endothelial cell and that type coming from the spinal canal proper are usually quite different. (See Hough, Government Hospital for the Insane, Bulletins 1, 2, 3.)

Unknown and degenerated cells need no description.

Other authorities describe as many as six or seven types of cells in cerebrospinal fluid, and Hough, using the Alzheimer method of examination, reports eight to ten different types, with as many varieties for each type. The small

lymphocyte is, however, recognized as the same by all, and, since about five cells per cubic millimeter are recognized as normal and the larger percentage of cells found here are of this type, it clearly indicates that there is an increased lymphocytosis in the cerebrospinal fluid of pellagrins. We are now studying other cases, and hope to have in the near future at least 150 or 200 cases to report upon.

All authorities concede that the differential count is more or less variable, depending upon each worker's idea of the different cell types. W. H. Hough, Bulletin No. 2, Government Hospital for the Insane; F. W. Mott, *Lancet* (London), July 29, 1910; and J. V. May, Binghamton, State Hospital Report, point out that a positive butyric acid reaction as originally suggested by Noguchi (Serum Diagnosis of Syphilis, first and second edition, 1910, 1911) is not specific for any one disease. We can confirm this, as in all cases of pellagra and also in others examined we have obtained an increase in the globulin content, as evidenced by a flocculent precipitate, often heating 0.2 cubic centimeters spinal fluid with 0.5 cubic centimeters of 10-percent solution pure butyric acid in normal (0.9-percent) saline solution, adding 0.1 cubic centimeters normal sodium hydrate and reheating. Precipitates of varying degrees occur from a few flocculent particles to a dense one which covers the bottom of the tube after settling. The butyric acid test is, however, to a certain extent a control on the microscopical findings, as those specimens with a low cell count invariably show weak butyric acid reaction.

All specimens examined were alkaline in reaction, and reduced CuSo4 in alkaline solution. Benedict's one solution reagent was used for testing reduction of CuSo4, as we believe, after comparisons with Fehling's, it is more reliable and also saves considerable time. To 1 or 2 cubic centimeters of this reagent about 0.3 cubic centimeter fluid were added and mixture heated for one-half to one minute, when a yellow or reddish yellow precipitate occurred.

PAIN.

The pains in pellagra resemble to a degree the pains of neurasthenia. These pains are variable and transient, like the pains so often complained of by a chronic neurasthenic. They are more common during the attack in the initial stage and during the whole of the second or neurasthenic stage. They are most common in the back, and resemble those cases of painful spine following railway accidents and other injuries in a traumatic neurasthenic. Tenderness may occur rarely the whole length of the spine, but usually it is more common in the dorsal region, and the tenderness is often greater on one side. Sandwith, in 178 cases, found pain absent in 59, pain in the whole back in 42, pain between the first and fourth dorsal vertebra in 12, between the fifth and eighth dorsal in 35, between the ninth and twelfth in 17, and 13 had pain in the lumbar region. In only 19 of the whole number was the pain symmetrical.

In Egypt the back pains occur in about one-third the cases, and is a symptom that disappears. This pain may vary from tenderness on pressure to an actual hurt on walking, rising, or sitting. The pains may radiate down into the hips, though actual coccygodynia is rare. Siler found spinal tenderness present in 14 of the Illinois asylum cases. In Italy commonly and in America more rarely the pain is so severe as to cause the pellagrin to walk bent over and with his spine held rather stiffly to reduce the pain. I saw one negress recently between attacks and apparently in good physical condition, yet the pain in the back persisted and the walk was stooped and careful. The tenderness elicited on pressure is to one or the other side of the spinous processes. (Watson.)

These pains are by no means confined to the back, but may even be absent in the back and occur elsewhere. Headache occurs, but it is more common in the early onset and is not usually severe. The burning pains have been discussed in the chapters on the Alimentary Tract and the Skin. They occur more often in the extremities and the stomach, but are occasionally more widely distributed. Gastralgia has also been referred to. Pains are occasionally complained of in the hips and feet, and there may be a general hyperesthesia, with pains and soreness "all over," as in influenza. Pains in the joints are rare.

REFLEXES.

Exaggerated knee jerks characterize pellagra in its early stages. There are exceptions to this rule in late cases, and occasionally in those of Hyde's type B, with posterior tract degeneration to a marked degree. In private practice, in cases preceding insanity and without a severe involvement of the cord, the knee jerk is practically always increased. It is often pronounced, like the knee jerk in hysteria in a young woman. The slightest tap of the tendon will cause a pronounced response, and with repeated taps the responses are so exaggerated that the leg is kept nearly extended and the foot in the air. In early cases the exaggerated knee jerks and the exaggeration of other reflexes, like the elbow, are due in large measure to the neurasthenic condition of the patient, the blow his vitality has received from the disease, and the hypersensitive condition of the nervous system. Later the organic tissue changes occur in the cord; confined to the posterior column, the reflexes

are diminished or absent, analogous to locomotor ataxia; confined chiefly to the direct pyramidal tracts, the reflexes are exaggerated, analogous to ataxic paraplegia and the escape of the posterior root zones in that disease; with the involvement of the posterior columns and the lateral columns, the reflexes are at first increased, and later may decrease or be absent. This last condition is similar to the subacute degeneration of the cord or diffuse degeneration of the cord as described by Putnam, and in which there is persistent parasthesia, weakness, rigidity, and pain in the back.

In the early stages of the disease these knee jerks are exaggerated more during the attack and less in the intermission. A knee jerk may be increased during the attack and then return to normal as the attack recedes. This is shown very well by Sandwith's comparative figures. In 165 cases studied during their hospital stay, only 3 had normal jerks, increased in 48, extremely increased in 76, diminished in 15, and absent in 23. After treatment and improvement at the hospital, 129 of his cases showed normal knee jerks in 10 percent, slightly increased in 54 percent, extremely increased in 10 percent, decreased in 12 percent, and absent in 8 percent. Siler's cases among the insane showed knee jerks normal in 20 percent, increased in 62 percent, and decreased or absent in 18 percent. Occasionally the jerks vary on the two sides. Tucker reports a case of this kind, and I saw one such case in Italy. Tucker had increased reflexes in 40 out of 46 cases.

Ankle clonus is rare, and present only in advanced and incurable cases. It is more frequently seen in the asylums than in private practice, and is often asymmetrical. The asymmetry follows the asymmetry in the patellar reflex, changes in the elbow reflex, the Babinski reflex, and the reflexes of the skin. The Babinski is more common than the ankle clonus, and in turn may be asymmetrical, present on one side and absent on the other, or more exaggerated on one side than on the other. It is found chiefly in the insane, the advanced, and in the acute and cachectic forms. Siler tested this in the Illinois cases and found the plantar reflex normal in 32 percent, increased in 53 percent, and diminished in 15 percent. The skin reflexes show variation in elevation or absence. The pharyngeal reflex is usually decreased. In general it may be said that the knee jerk is the most important and the elbow reflex usually follows the knee type. With knee jerk, Babinski, and clonus the case is advanced and serious. The early presence of the knee jerk

and its gradual disappearance indicates increasing changes in the cord.

CHANGES IN THE MUSCULAR SYSTEM.

In about half the cases of pellagra the muscles show atrophy, and occasionally fatty degeneration. There is a greater percentage of asylum cases with pronounced muscular atrophy than in cases seen in private practice. Out of 44 cases, Lombroso found atrophy in the muscles in 21. The muscles are pale from lack of blood, and the entire muscular system is in a state of malnutrition, lacking the vivid vitality and strength of normal muscle. It is evident that muscular weakness is the natural result of these changes, and, with the progress of the disease and the rather sedentary life of the advanced cases, the atrophy and weakness tend always to increase. Even in those cases without atrophy the muscular strength is decreased, and the inability to keep pace with the healthy is apparent. This weakness of the muscles attacks preferably the lower extremities, and in the upper extremities shows a selective action for the extensors, with resulting overaction of the flexors and accompanying contractures. The extensors get into a state of paresis, so that the limbs are in a state of semiflexion owing to a preponderance of the flexors, and remain fixed or resistant when an attempt is made to move them. (Hirsch.)

Tucker's cases show muscular atrophy in 35 out of 52 cases, and muscular weakness in 49 out of 53 cases. The electrical excitability of the muscles is very little changed, though the flexors of the forearms are more easily excited than the extensors. Reaction of degeneration is usually absent. The greater excitability of the flexors is explained by the paretic tendency of the extensors, which leads to contractures in the hand. On mechanical stimulation, incomplete muscular contractures and fibrillary twitchings occur, indicating the weakness both of the muscles and the centers of the innervation. This response to mechanical stimulation is evidently due to the irritation of the peripheral nerves from the circulating toxin, analogous to the marked and incomplete contraction of the biceps in typhoid fever, according to the recent test noted by Burke, of Iowa, though this condition is really a nodular myoidema.

With this atrophy or muscular weakness gradually progressive as the disease advances, and the ever-increasing organic changes in the cord and brain, tremors, cramps, contractures, uncertain

and painful gait, rigidity of certain groups, with stiffness of adjacent joints, develop with great variability in different cases. Tremor is more common during the attack, and in advanced cases accompanied by a pellagrous psychosis. It may occur rarely all over the body, but is usually more common in the upper half of the body and there more often in the hands; then the tongue, lips, and face in order. According to Cabot, tremor is a clonic spasm of short duration, and its cause here is the toxemia, weakness, and neurasthenia. It is best seen, when present, by asking the patient to put out his tongue as far as possible or extending the hand with the fingers wide apart. I have seen the facial muscles exhibit tremors in pellagrins, one clonic contraction following another rapidly. Such a condition is more common during the acme of the attack. After exercise in pellagrins, even between attacks, these tremors are accentuated, especially when great weakness is present.

A cramp is a local spasm of a muscle or a muscle group—a kind of epilepsy of a muscle. It occurs often during sleep, and more frequently during the night, when the conscious control of the mind is absent. It characterizes neurasthenia and states of chronic exhaustion. In pellagrins it is common. Tucker's admirable questions on this point gave cramps in 28 out of 52 cases; in 9 they were in the abdomen, and in the other cases in the arms, hands, legs, back, and in 3 cases they were general.

After several attacks, or occasionally after one attack, as in Elrod's case, the muscles lose their elastic tone and become rigid, with accompanying stiffness of the joints covered. These contractures concern chiefly the flexors of the arms and legs. Fig. 62 shows the permanent contraction of the little and ring fingers of the left hand following one severe attack in the spring. These fingers were flexed on account of the paresis of the extensors, and were extended only slowly and with difficulty. The thumb may be contracted across the palm, or the arms carried drawn up. In these advanced cases one is often struck by the stiffness of the legs when the patient sits and when an attempt is made to relax the lower extremity. The foot is held half extended and the leg stiff, like in a spastic paraplegia. This rigidity of the muscles is pronounced during an attack, especially in a cachectic condition. The pellagrin lies in bed with the feet drawn up and the thighs flexed on the abdomen. In one case this position was maintained for a month. Here, too, the foot is often flexed and the ankle joint is

stiff, and the foot moves with difficulty. The pellagrin in this condition is unable to quickly relax the flexor muscles.

With muscular atrophy and weakness, stiffness of the joints, spinal tenderness, and rigidity, the natural walk is changed. This is true only of the advanced cases with pronounced cord changes, emaciation, paretic conditions, or marked weakness of the entire body. In the vast majority of pellagrins the walk is natural and easy, and especially is this true the greater part of the year between the attacks. Even as the disease advances, the only variation from the normal walk is an increased slowness and a slight stooping of the shoulders. In the advanced cases, with changed walk, there is a combination in the different cases of slowness, ataxia, spastic walk, and simple weakness. These vary according to the condition of the pellagrin and the tracts of the cord chiefly affected. As a rule, the paretic gait is in evidence. The legs are kept well apart, the shoulders raised and bent forward, the body inclined more to one side than the other, and falling is so easy that a staff is necessary. The patient rises with care, and the first few steps are taken slowly and as if the feet were hunting for the ground. Vertigo adds to this fear of falling, and the patient "must get started right" before he walks even easily. The feet are kept farther apart than normally, and put down with care. The knees are more flexed than usual, and the legs lack the natural swing of health and vigor. Following paralysis, the gait becomes hemiplegic, and occasionally there is a tendency to fall forward or backward.

Paralysis occurs, but it is not common, and is seen chiefly in advanced cases in the asylums. Preceding death, meningeal symptoms develop in a few cases, with tetanic and choreic movements, epileptiform attacks, and even an occasional convulsion. Kernig's sign may be present in such cases, with clonus and spasticity. During the convulsive seizures or the meningeal rigidity the pupils are apt to be irregular and act independently one of the other, or with external or internal deviation. At this time wrist drop is seen, paralysis of the sphincters, with incontinence of the urine and feces, and delirium. Bedsores are rare.

Insomnia is a prodromal sign which characterizes many cases in the period of onset of the attack, and the insomnia in such cases is increased during the outbreak. As the disease progresses and neurasthenia develops, sadness, silence, and sleeplessness increase. The voice changes from the natural, modulated human voice to

an undertone of monotony and sadness. It is a monotone on a low level. In this neurasthenic stage the pellagrin talks very little, and often one of the first complaints heard in the morning is the lack of sleep the previous night. His nervous condition is attributed to the inability to sleep, and the physician is told, "If I could only sleep, I would be all right." Sandwith observed sleep

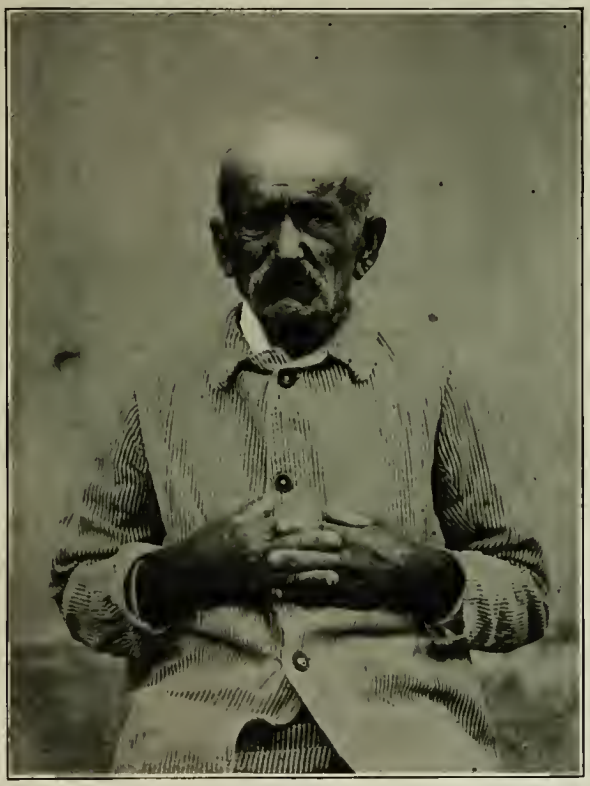


Fig. 54.—Pellagrous insanity. Dermatitis on hand, with exfoliation of the skin. (Courtesy of Dr. Bravetta.)

in 150 pellagrins; 40 percent of them slept normally, 23 percent six hours, 19 percent four hours, and 18 percent less than three hours in the twenty-four. This is in Egypt, where the nervous phenomena are not as pronounced as in Italy or America. All of my cases have complained of insomnia at times, and of "just lying awake" during the night.

At first the mental condition is not affected, and after one or

two annual attacks, or indeed after several mild attacks, with the patient still in the initial degree of the disease, the mental condition remains normal, the spirits cheerful, and the mind may maintain its normal vigor. With the progress of the chronic form, or the rapid advance of the acute and subchronic cachectic forms, the mental processes become retarded. The transient headaches of the beginning are gone, and instead dizziness, noises in the ears, neurasthenic sensations of weight, lightness, and distinct pulsations increase the introspective wondering of the pellagrous neurasthenic. The causes of these varied symptoms in the head are not so clear. The whole brain in pellagra is in a state of malnutrition, and this is accentuated as time goes on, both by the increasing organic changes taking place in the brain and the cord, and by the inability of the whole system to gain from the food the desired fuel and substances for repair. These ingredients are in the food, but the poison of pellagra prevents the system from taking advantage of them. Pellagra places in the nerve cell a poison of some kind, and takes from the nerve cell its power of self-nutrition. In short, pellagra exhausts the nervous system.

The vertigo, noises, and roaring in the ears are causally related to each other. The basic cause is the lack of ability of the brain to overcome the poison and to nourish itself. Added to this are the changes in the cortical and the cerebellar cells. The exhaustion of the whole brain, or cerebrasthenia, can of itself cause these symptoms. As pointed out by Beard, in exhaustion of the brain there often occurs a hyperesthesia of the auditory nerve like the hyperesthesia of the optic nerve in the same disease, both of which are inconstant, variable, and capricious, and that without organic tissue changes in the auditory nerve. Vertigo can result "from affection of the higher cerebral centers, or of the coördinating cerebellar centers, or from affection of any of the afferent paths, as from the semicircular canals. (Purves Stewart.) In advanced cases the ataxia may be due to the cerebellar changes, but earlier in the disease the vertigo and noises in the ears are more to be accounted for as neurasthenic symptoms than otherwise. Indeed, the noises in the ears are often complained of as a prodromal symptom developing before the dermatitis. I have found no report of any tissue changes in the auditory ganglia or in the auditory nerve, but a research in this locality might throw additional light on these symptoms.

Neurasthenia is the vitiated soil that spreads over the body as it takes the down trail of emaciation and weakness. These recurring attacks of dyspepsia and indigestion, of oral rawness and rectal soreness, these diarrheas that come in the spring, leave stretches of bareness in the nervous system, both in respect to the vigor of the mind and the organic wholeness of the nerve tissue.

Fig. 55.—Pellagrous insanity. Dermatitis on hands. Period of recession. Note expression on face. (Courtesy of Dr. Bravetta.)

These recurring involvements of the abdominal ganglia of the sympathetic system make their impress on the mind, and the pellagrin becomes conscious of all his abdominal organs. The pellagrous neurasthenia begets introspection, and the introspection begets hypochondria, and hypochondria begets permanent sadness. The smile of life has gone and the set of despair has come. Imagine the condition of the pellagrin as he himself views his condition.

The complaint of this patient relates to the gradual disintegration of his body and of his mind.

For one or two years, or even a few years longer, he stood his disease very well. Then the strange feelings in his head common during the attack begin to be permanent; the head is light or full, dizzy sensations come, he must rise slowly lest he fall, his legs seem weak, and walking is slow and careful. He has been growing worse all these years instead of better. His hope is beginning to leave him—his mind goes slowly like his feet. He can no longer think quickly as formerly. His thoughts are few and slow, and he is no longer certain of himself. Like Napoleon in his last illness, each pellagrin begins to feel that he "can no longer unbend the bow." He is no longer himself. Memory begins to waver, and the recent past is more like an impotent dream. The lines and letters run after each other on the page, so that he can hardly use his mind to read. Formications, burnings, creepy feelings, coldness, numbness, run over the skin. The muscles of the legs seem rather lifeless, and the feet lift like lead. His vision is that of an old man, his face is thin, and his brow wrinkled a score of years before its time. He fears men, and grows silent. His thoughts are gone, and he can no more supply his tongue with many words. Neurasthenia, sadness, hypochondria, edge on melancholy, and the mind begins to lift its tent and steal away.

Pellagra is a disease of the body, but in a majority of the cases it involves the mind to a greater or less degree. The somatic disintegration usually precedes the psychic disintegration; but the more the advance of the former, the greater the give of the mind. Even in the neurasthenic stage, with the mind in comparatively good condition, on close examination there will be found:

1. A simple retardation of the mental processes.
2. Impairment of memory.
3. A general feeling of depression.

The stream of consciousness is slowed, and new ideas are incorporated with great slowness. Memory is poor, and old impressions rise to the surface with difficulty, or not at all. The number of points of contact is decreased, and there is just mind enough for a very limited number of ideas. What mind there is moves with exceeding slowness. There is no better illustration of this than the inability of the pellagrin to answer easy questions. Jansen was impressed with this, and wrote in his Latin treatise,

"Interrogatæ vix respondebant"—when asked questions, they responded with difficulty. Furthermore, what questions they do answer come in monosyllables in a monotone and with hesitation. Even such a simple question as "When did you wake this morning," or "How far do you live from town," seemingly causes an effort to comprehend or to answer. I have also noticed that what is answered is put in an indefinite and noncommittal way. The pellagrin seems totally unable to incorporate a definite idea, to consider that idea, and to give a definite response to the idea as considered. Probably his poor memory has something to do with this. I have seen one apparently in good mental condition, and well orientated to his environment, look appealingly to his brother on being asked how far he lived in the country, and, again, how long he had been sick, and yet he had just been describing his condition and where he lived. This illustrates his inability to associate ideas, to form new concepts, and to sort the usual run of perceptions. The pellagrin loses his idea of the passage of time. He comes into the consulting room, sits, looks, listens, says little, and seems to have no idea of moving or going. Added to his mental inertia is his chronic depression. His dermatitis and diarrhea have left this depression in their wake. The world resolves itself into his slowly uttered account of his own history and condition.

PSYCHOSES ACCOMPANYING PELLAGRA.

Dr. E. M. Green, clinical director of the Georgia Asylum for the Insane at Milledgeville, has given me the facts and cases on the psychoses accompanying pellagra, which follow:

From January 1 to November 1, 1911, there were admitted to this asylum 60 cases which presented evidence of pellagra on admission. The mental condition as well as the physical condition of these were studied in detail by Dr. Green and his corps of staff physicians, and the resulting facts grouped and related by Dr. Green. It is well to present these in the form of summaries, and to give an illustration of each of the types as classified.

It is estimated that about 10 percent of the pellagrins in Italy are insane. It is impossible to make an estimate as to the relative number in America on account of the inability to obtain the exact number either of the pellagrous or of the pellagrous insane. I am disposed to think it would be far under 10 percent of the whole

number, and that 5 percent would be nearer. There is a distinction just here pointed out by Warnock in his 1909 report when he writes: "These figures refer to cases of insanity due to pellagra—not to cases showing pellagrous symptoms merely. Thus we admit numbers of congenital imbeciles, precocious dements, epilepties, and senile dements who have signs of pellagra, but their pellagra seems a coincident illness—not a cause of the insanity; so their diagnosis would appear under other headings." He ranks pellagra as a cause of insanity along with syphilis, alcohol, and hashish. It is evident, then, that (1) one may have pellagra and not be insane; (2) one may be insane from causes other than pellagra and later develop pellagra; (3) one may be insane with pellagra as the direct cause. This present discussion considers chiefly the last group.

The physicians in the asylums of the country see pellagrins from the standpoint of the mind first and the body afterward; the physicians in private practice see pellagrins from the standpoint of the body first and the mind afterward. The asylum physician meets the pellagrin with his mind gone; the physician outside sees the pellagrin until the mental disintegration ensues, and, although the patient goes to the asylum mentally disabled, he is a pellagrin, with the disease still in evolution. It is well for each group of physicians to get the point of view of the other, and each group gains evidence from experience on the disease. Outside the asylum the disease presents many of its lesser phases; inside it presents the accentuated phases. There is no finer lesson in pellagra than to see and examine the pellagrins in the asylums, and one is at once compelled to enlarge his horizon of the manifold character and variability of the pellagrous syndrome.

The classification of the psychoses accompanying the disease is important. One of two courses is open—either to add a new entity to the classification of insanity and call it pellagrous insanity, or, viewing pellagra merely as one of the causes of insanity, refer to pellagra with its accompanying psychosis, and the psychosis is classified according to the type which the symptoms in their sum total indicate. This is best stated by Dr. Green in regard to his own cases:

> The mental picture which these cases present is not uniform, and I do not believe that at present we can recognize "pellagrous insanity" as an entity. Temporarily, at least, I think it best to place them under the general heading

of "psychoses accompanying pellagra," and to subdivide this group into the different types which the mental symptoms seem to indicate. If the mental symptoms are those of dementia precox, the subdivision should be "dementia precox type." If the mental symptoms are those of infective exhaustive psychosis, the subdivision should be "infective exhaustive type," and so on through the different types.

There exists no combination of mental symptoms which at present we can

Fig. 56.—Pellagrous insanity. Dry dermatitis, with exfoliation of the skin. Face sad and serious; brow wrinkled and puckered. (Courtesy of Dr. Bravetta.)

recognize as being peculiar to pellagra alone. Many forms of psychosis may accompany this disease—the latter being the chief, possibly the sole, etiological factor. These cases are grouped under the general heading, "psychoses accompanying pellagra," which is subdivided into types as the symptoms noted seem to approach those of the recognized forms of insanity.

1. The largest of these subgroups is the "infective exhaustive type." It is characterized by the symptoms found in other infective exhaustive psychoses,

and may appear as acute delirium, amentia, or chronic nervous exhaustion. The symptoms most commonly found in this type are clouding of the consciousness, confusion, delirium, apprehension, restlessness, and hallucinations.

2. The next largest of the subgroups is the "dementia precox type." In this the patient may appear apathetic, seclusive, inattentive, negative, and deteriorated. Mannerisms, stereotypes, neologisms, impulsive movements, and cries may be noted. Delusions of persecution, poison, and influence may be expressed, and hallucinations are usually present. These cases may show the hebephrenic, katatonic, or paranoid forms observed in other cases of dementia precox.

3. The "manic depressive type" is less frequently met with. It usually takes the depressed form, in which are observed depression, decreased psychomotor activity, and difficulty in thinking. Ideas of insufficiency, sin, with self-reproach, and a tendency to suicide are not uncommon, while hallucinations are usually present. The manic form presents the usual manic symptoms of elation, increased psychomotor activity, flight of ideas, distractibility, excitement, and boisterousness.

4. In the "general paralysis type" are found the usual physical signs accompanying that disease. These consist of disturbance of sensation, increase or loss of deep reflexes, inequality or irregularity of the pupils, disturbed pupillary reaction to light, tremors, unsteady gait, and speech disturbances. The accompanying mental picture is usually that of dementia.

5. The "involutional melancholia type" appears after middle life, and presents an agitated depression, with ideas of unworthiness, sin, and self-reproach. Suicidal tendencies are marked and auditory hallucinations are frequent.

6. The "senile dementia" type is seen in those who have reached the middle period of life, and offers the usual symptoms of this condition. Here are found increased irritability, aimless wandering, unreasoning resistance, disorientation, with memory disturbance, and often accompanied by confusion and hallucinations.

7. The "unclassified type" represents a large number of cases. The symptoms are either indefinite, can not be elicited, or are of such character that they simulate no recognized form of psychosis, nor have they enough in common to form a separate group.

From January 1 to November 1, 1911, Dr. Green and his staff studied 60 cases which presented evidence of pellagra on admission. These were classified according to the "type of psychosis" as follows:

Infective exhaustive	30
Manic depressive	9
Dementia precox	9
General paralysis	2
Senile	3
Involution melancholia	2
Unclassified	5
	60

CASES ILLUSTRATING EACH TYPE OF PSYCHOSIS.

Infective Exhaustive Type.

M. J. G., white female, aged 42, married, domestic servant. Has had one previous attack of insanity.

Fig. 57.—Pellagrous insanity in the aged. Face wrinkled, puckered, and drawn; hands cracked and dry; increase of wrinkles over finger joints. Typical expression. (Courtesy of Dr. Bravetta.)

Duration of pellagra is eighteen months. The duration of insanity is twenty-three days. The evidences of pellagra are wrinkling and roughening of the skin on the back of the hands. There is abdominal tenderness, and eighteen months ago there was stomatitis, diarrhea, and eruption over the

back of the hands. The only complication is an apical systolic murmur. The termination was death.

The nervous symptoms were muscular strength diminished, deep reflexes exaggerated, pupils react sluggishly to light, sphincters not controlled, speech slurring, Babinski sign uncertain, and ankle clonus was not constant.

The mental symptoms were delirium, confusion, restlessness, agitation, incoherence, apprehension. There were hallucinations of hearing, and disorientation for time, place, and person. Memory was poor for both recent and remote events. Retention was impaired, and grasp on school knowledge and general information was poor. Counting and calculation defective. Attention can not be held. Insight lost. Judgment much impaired.

The Manic Depressive Type.

E. C., negro female, aged 33, widow, farm laborer. The duration of her pellagra is unknown, and she has been insane one month. The skin is darkened on her wrists, dorsa of her hands, and lower third of her forearms. There are pigmented spots on her face, chest, and back. Her tongue is red, and there is stomatitis and vaginitis. The labia are red, with denuded areas and a whitish deposit. The abdomen is rigid and there is constipation. No complications.

The nervous symptoms are subjective complaints of vertigo, numbness of hands, and sensations as if pins were sticking into the skin. The facial muscles were weakened and the face drooped. The deep reflexes were exaggerated and there was coarse tremor of the fingers. The tongue showed a fine tremor, with speech sticking and slurring.

The mental symptoms showed depression and slowness, speech in an undertone and not spontaneous. Ideas of sin present, self-reproachful, with suicidal tendencies. Hallucinations of sight and hearing, with a history of excitements, during which it was necessary to tie her. Orientation undisturbed and memory preserved. Retention defective, but counting and calculation good. Insight fairly good. Judgment impaired.

Termination, death.

Dementia Precox Type.

S. S., negro male, aged 30, single, no occupation. Duration of his pellagra is unknown and his insanity has lasted six months. There is a darkening and roughening of the skin on the back of the hands, wrists, elbows, and feet. The tongue is fissured and diarrhea is present. Syphilis exists as a complication.

The nervous symptoms are headache, muscular weakness, all deep reflexes exaggerated, fine tremor of tongue and fingers, and twitching of muscles about eyes and mouth.

The mental symptoms are apathy, inattention, contradictory replies, grimaces, impulsive movements and replies, mannerisms, seclusive and not spontaneous. Ideas of influence, persecution, poison, neologisms. Hallucinations of sight and hearing. Orientation disturbed for time. Memory fairly good for both recent and remote events. Retention defective. Grasp on

school knowledge and general information good. Counting and calculation good. Insight partially preserved and judgment defective.

Termination, death.

General Paralysis Type.

M. R., wife of a business man, aged 48. Duration of pellagra unknown and insane for last three months. There is reddening of the skin over the knuckles, scaling of the epidermis from the elbows, and especially on the dorsal surface of the hands and forearms. The abdomen is full and tender on pressure. There are no complications.

The nervous symptoms are muscular weakness, vertigo, temperature. Sense impaired in the lower extremity. Deep reflexes are exaggerated. Incoördination of voluntary movements. Gait careful. Tremor of tongue. Pupils irregular and somewhat sluggish to light. Speech has slight defect.

The mental symptoms are apathy, hallucination of sight, orientation disturbed for time. Memory is impaired both for recent and remote events. Retention is poor. Grasp on school knowledge is defective. Counting fairly good. Calculation lost. Insight absent. Judgment poor.

Termination, still under treatment.

Senile Dementia Type.

K. G., laborer, aged 65 years. He has had pellagra seven months, and been insane two and one-half months. He has the skin lesions of pellagra on his knees and back of his feet, and his hands are very rough and pigmented. His tongue and buccal mucosa are very red and diarrhea exists. There are no complications.

The nervous symptoms show arcus senilis, muscular weakness, knee jerks increased. The abdominal and cremasteric reflexes are absent. The gait is unsteady.

The mental symptoms show irritability. He wanders aimlessly round the ward, unable to find either his room or the dining-room. He is slightly resistive and demented. There is disorientation for time, place, and person. Memory for remote events much better than for recent ones. Retention is poor. He counts fairly well, but can not calculate. General information fairly well preserved. Insight absent and judgment very defective.

Termination, death.

Involutional Melancholia Type.

M. S., wife of a farmer, aged 53. The first attack of pellagra was in 1908, the second in 1909, and the third in April, 1911 (five months ago). She has been insane for three months. There is roughening and pigmentation of the skin on the back of the hands and wrists, and extension around the wrists to the anterior or flexor surface. There is some scaling. Arteriosclerosis complicates this case.

The nervous symptoms are subjective complaints of headache, vertigo, weakness, precordial oppression, fullness of head, hot and cold flashes. The skin is dry. Hearing, sight, and smell are impaired. Temperature sense

diminished. Muscular weakness. Deep reflexes are exaggerated, the plantar diminished, and the pupils react sluggishly to light and accommodation. The consensual reflex is absent.

The mental symptoms are depression, and she is anxious, agitated, suspicious, and somewhat confused at times. Delusions exist. There are hallucinations of sight and hearing. Orientation is impaired. Slight insight. Judgment impaired. Owing to lack of coöperation, retention, memory, etc., not tested satisfactorily.

Termination, still under treatment.

Unclassified Type.

F. G., negro woman, aged 30, unmarried, agricultural laborer. The duration of pellagra is unknown, and she has been insane for two weeks. The skin is dry and pigmented over the backs of the hands, the buccal mucosa is inflamed, tongue is red, fissured, and raw. Vaginitis is present, and probably syphilis.

The nervous symptoms are muscular weakness, deep and superficial reflexes exaggerated, sphincters not under control.

The mental symptoms are indifference, and unusually destructive, filthy, noisy, and restless. Inaccessible to examination.

Termination, death.

ANALYSIS OF CASES.

The following is an analysis of the sixty cases presenting evidence of pellagra on admission, and from which the preceding type cases are taken. These summaries are made by Dr. Green, and furnish much information hitherto unavailable in the study of the mind in pellagra.

RACE AND SEX.

White male	14
White female	22
Negro male	7
Negro female	17
	60

CIVIL CONDITION.

Married	42
Single	12
Widowed	5
Separated	1
	60

AGE.

Average	38
Youngest	18
Oldest	69

OCCUPATION.

Farmer	10
Farmer's wife	10
Farmer's daughter	1
Farm laborer	11
Farm laborer's wife	1
Domestic	8
Housekeeper	3
Minister	1
Miller's wife	1
Locomotive hostler	1
Plumber's wife	1
Salesman	1
Salesman's wife	1
Seamstress	1
Mill operative	2
Merchant's wife	2
Stone cutter	1
Laundress	2
Machinist	1
None	1
	60

DURATION OF PELLAGRA.

Number of patients	30	
Average duration	8½	months
Shortest	1	month
Longest	4	years

DURATION OF INSANITY.

Average duration	7 months, 1 week
Number of patients	57

COMPLICATIONS.

Number of patients	31
Pulmonary tuberculosis	10
Syphilis	5
Valvular heart disease	10
Arteriosclerosis	6
Chronic nephritis	1
Enlarged thyroid	2
Bronchitis, chronic	1
Drug habit	1

TERMINATION.

Death	29
Recovery	6
Recovery from pellagra, mentally improved	3
Removed unimproved	1
Remaining under treatment, November 1, 1911	21
	60

Summary of Nervous Symptoms.

SUBJECTIVE COMPLAINTS.

Headache	23
Vertigo	20
Weakness	8
Pain	10
Formication	6
Numbness	7
Nervousness	10
Illness	6
Indigestion	3
Precordial distress	6

IMPAIRMENT OF SPECIAL SENSES.

Vision	3
Hearing	8
Smell	9
Taste	2

DISTURBANCE OF SENSATION.

Hypesthesia	3
Hyperesthesia	2
Anesthesia	1
Temperature sense (impaired)	6
Stereognostic sense (impaired)	1

MUSCULAR CONDITION.

Weakness	42
Rigidity	6
Twitching	9
Contracture	1
Incoördination	12

REFLEXES.

Deep.

Exaggerated	42
Diminished	7
Absent	2
Tremor	45
Ankle clonus	7
Convulsions	1
Sphincter weakness	15
Tenderness of muscle and nerve trunks	6
Rhomberg's sign	9
Babinski's sign, both sides	5
Babinski's sign, right side only	1

Superficial.

Exaggerated	5
Diminished	3
Absent	6

Pupillary.

Sluggish	9
Consensual absent	1

GAIT.

Unsteady	17
Spastic	1
Hemiplegic	1

SPEECH.

Indistinct	2
Sticking	10
Slurring	14
Drawling	3
Thickened	1
Disturbed	5

Summary of Mental Symptoms.

Depression	25
Retardation	15
Suicidal	13
Exaltation	6
Irritability	9
Distractibility	3
Flight of ideas	2

Volubility	5
Boisterousness	12
Restlessness	17
Excitement	8
Violence	10
Erotic	1
Obscene	1
Profane	1
Confusion	22
Apprehensiveness	26
Destructiveness	7
Suspiciousness	5
Inaccessibility	5
Fabrication	3
Incoherence	6
Apathy	11
Resistive	9
Negative	3
Mute	7
Seclusive	3
Not spontaneous	7
Irrelevance	4
Contradictory statements	1
Catalepsy	6
Refusal of food	5
Mannerisms	5
Impulsive acts	1
Change of personality	2
Drowsy	2
Filthy	9
Mumbling	4

DISORIENTATION.

For place	2
For time	8
For time and person	3
For time and place	4
For time, place, and person	26

MEMORY IMPAIRED.

For recent events	3
For remote events	1
For recent and remote events	25
More for recent than for remote events	4
More for remote than for recent events	6

RETENTION.

Impaired	34
Lost	11

GRASP ON GENERAL INFORMATION AND SCHOOL KNOWLEDGE.

Impaired	16
Much impaired	18

COUNTING.

Impaired	17
Lost	3

CALCULATION.

Impaired	25
Lost	9

ATTENTION.

Much impaired	16

INSIGHT.

Impaired	20
Absent	25

JUDGMENT.

Impaired	27
Much impaired	25

HALLUCINATIONS (NUMBER OF PATIENTS, 41).

Visual	3
Auditory	14
Visual and auditory	24

DELUSIONS.

Expansive	3
Depressive	18
Persecutory	34
Influence	4
Not stated	3

When it is remembered how great are the changes in the individual cortical cells as stated by Spiller, the mental failure in pellagra is easy to understand. It would seem in pellagra, as in tabes, that the changes in the brain vary in different cases.

DURATION OF HOSPITAL RESIDENCE BEFORE EVIDENCE OF PELLAGRA WAS NOTED.

The following is a list of cases of pellagra reported in the Georgia State Asylum from January 1, 1911, to November 1, 1911, which showed no evidence of the disease on admission.

Under 2 weeks	5
2 to 4 weeks	4
4 to 6 weeks	5
6 to 8 weeks	3
2 to 3 months	7
3 to 4 months	5
4 to 6 months	10
6 to 9 months	6
9 to 12 months	3
12 to 18 months	4
18 months to 2 years	4
2 to 4 years	13
4 to 6 years	8
6 to 10 years	8
10 to 15 years	1
Over 15 years	6
	89

CHAPTER VII.

OTHER SYSTEMS AND CHANGES.

CIRCULATORY SYSTEM.

The effect of pellagra on the circulatory system includes chiefly changes in the blood, both in the corpuscular elements and the hemoglobin content; a tendency to an increase in the pulse rate; a tendency to a decrease in the blood pressure; and, lastly, tissue changes in the heart itself. All these show great variation in different cases and in the different stages in these cases, but in general an attack accentuates them, and in the milder cases they are less pronounced during the intermissions. The blood is a tissue, although a fluid tissue, and it decreases in volume proportionately to the loss of weight of the body as a whole as the disease progresses. There are not only changes in the blood as commonly understood in medicine, but there is progressively less blood. The ever-recurring diarrhea removes appreciable amounts of blood serum, and more and more is this evident in the latter stages.

The principal change in the corpuscles is an increase in the percentage of the small lymphocytes, and this is usually accompanied by a decrease in the normal percent of polynuclear cells. This increase in the small lymphocytes is the one characteristic of the blood in pellagra. I give below two counts, the first of a woman 55 years old in the intermission period, up and about her household duties; the second was made by Low, of London, for Sambon, of blood from a 14-year-old, brought from Italy to London by the latter, during the recession of an attack. One is an American adult pellagrin, and the other an Italian child pellagrin, both females.

	American.	Italian.
Hemoglobin	80	95
White cells	4,500	8,400
Reds	4,184,000	4,850,000

DIFFERENTIAL COUNT.

	American.	Italian.
Polynuclears	52.6	56.
Small lymphocytes	33.	37.6
Large lymphocytes	13.	4.
Eosinophiles	2.	4.
Myelocytes	.6	0.
Transitionals	0.	2.

The American case had "some irregularity in shape and size of the reds, though the centers were fairly good." Three hundred white cells counted. Low's notes on the Italian case stated: "The shape and size of the red cells were good. In the differential count it will be noted that the small lymphocytes are relatively increased"—500 cells counted.

This relative increase in the lymphocytes was further borne out by fifteen differential counts in as many different cases, 500 leucocytes counted in each case. The counts were made by Low from cases brought from Italy by Sambon. When this excess of lymphocytes was absent, there was usually something to account for it, "such as polymorphonuclear leukocytosis due to sepsis or relative increase of the eosinophiles, in all probability due to ankylostomiasis." (Low.) My own cases show this relative increase in the small lymphocytes, but with no change in the large mononuclears.

Hyde reports 9 counts from the Peoria cases, with an average red count of 3,930,000, hemoglobin of 79.3 percent, color index of 1.01, leukocytes of 15,400, with an average differential count in the 9 cases as follows: polynuclears, 69.77 percent; small lymphocytes, 18.02 percent; large lymphocytes, 11.72 per cent; eosinophiles, .33 percent; basophiles, .16 percent. Hyde calls attention to the interesting fact that eosinophiles were found in only 4 of the 9 cases, and those only after counting several hundred leukocytes, and over a thousand leukocytes were counted in some cases without finding a single eosinophile. Lavinder, in South Carolina asylum cases, made 24 blood counts, with an average hemoglobin of 69 percent; leukocytes, 9,048; reds, 4,473,260. He made differential counts in several of these cases, with a relative increase in the lymphocytes and an absence of cosinophilia in the uncomplicated cases. Egan made 26 red counts in Illinois, with an average of 4,200,000; color index rather low, 1 or 0.9; occasionally microcytes

and rarely megalocytes; and several cases with an increased leukocytosis running up to 48,000 and down to 10,000. Buhlig, basing his clinical experience on the relation between the leukocyte

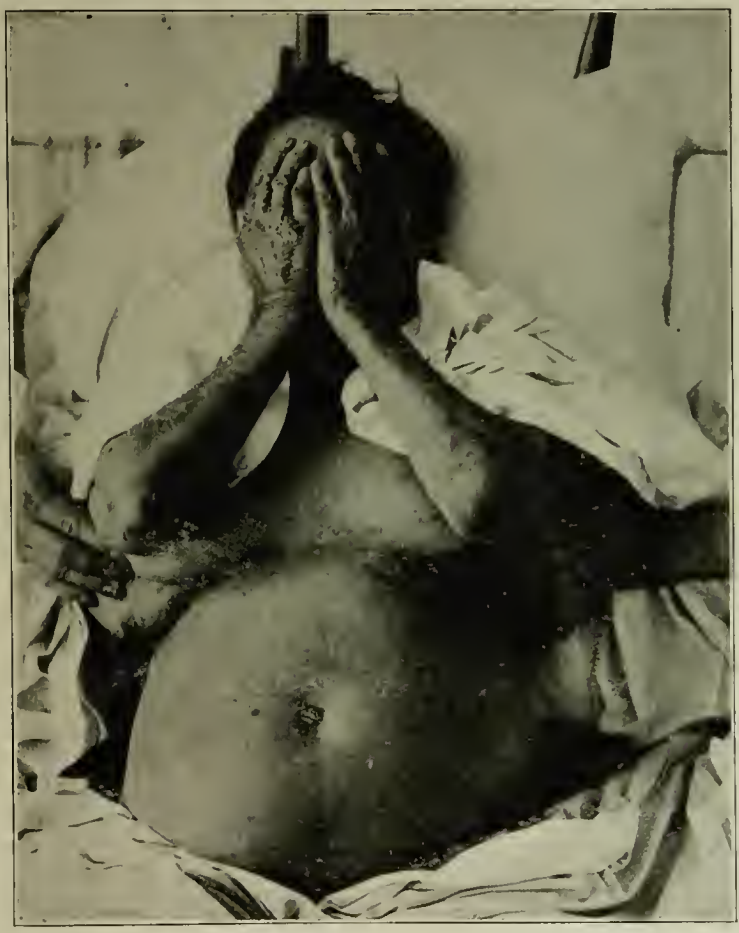


Fig. 58.—Pellagrin. A robust Irish woman. Dermatitis on hands, forearms, and elbows. Lesions under breast, probably due to pressure and sweat. (Courtesy of Dr. C. C. Bass.)

count and the outcome of the case, found that pellagrins with a high count die early.

The anemia in pellagra does not average as low as in hookworm infection. As a rule, it is not severe enough to produce a marked pallor, or the weakness, palpitation, and fever characteristic of

the more severe types of secondary anemia. If the percentage of hemoglobin runs as low as 75 or lower, one should suspect intestinal parasites, or some accompanying and anemic-producing infection. The anemia in pellagra is of a secondary type, after the manner of a chlorosis, with a qualitative change in the red corpuscles rather than a marked decrease in their number. The lack of coloring matter is evident on examination of the mucous membranes, especially of the mouth, and between attacks is apparent on the edges of the tongue. Tucker found this anemia noticeable in 42 out of 49 cases. The average hemoglobin percent in pellagra is near 80, though higher than this in the early stages and mild cases, and lower at times in the advanced stage or in the severe cases. The cause of this secondary anemia is found in the circulating pellagrous toxin and the accompanying disturbance of the body nutrition.

The tendency of pellagra is to increase the pulse rate. In all cases the pulse rate is increased during the attack, and, while in many cases it may return nearly to normal if the case be not too advanced, in by far the majority of cases it is permanently increased over its healthy normal. In a series of cases the following rates were noted:

1. Male, first attack, condition good .....pulse, 104
2. Female, advanced, in bed, cachectic .....pulse, 88
3. Female, advanced, in bed, neurasthenic .....pulse, 96
4. Male, first attack, in bed .....pulse, 100; standing, 110
5. Female, first attack, standing .....pulse, 96
6. Female, neurasthenic, sitting .....pulse, 90
7. Female, after five annual attacks, sitting .....pulse, 112
8. Female, first attack, rapidly progressive, sitting ....pulse, 90

For these 8 cases, taken at random, the pulse averages 98. In the very chronic cases common in Italy the rate is not so high, and even in the times of intermission it may run as low as 60 to 75. I have noticed, too, in the asylum cases, with the mind gone and body left in comparatively good state of nutrition, the pulse may be slow and full. Those insane pellagrins approaching cachexia show an advanced rate, and in all cases the character and rate of the pulse is an important prognostic sign. The faster the pulse, the more serious the single attack, and the continual increased rapidity of the pulse after the recession of the attack is ominous of the grave. When the pulse passes 100, the patient is on the

threshold of the danger line, and with a continued increase it may be taken as a certain sign of increasing peril. As death approaches, the pulse mounts, and after passing 130 it may be taken for granted that dissolution is not far off in the majority of cases.

As a rule, the pulse is regular, soft, and compressible, and, as the disease progresses, becomes of increasingly smaller volume. The emaciated wrist and strikingly rapid and regular pulse forms one of the clinical views of pellagra. With the decrease in the total systemic blood volume, the pulse decreases in volume, and becomes so small in the later periods of the malady that Procopiu has well called it the "filiform pulse." It is of wire smallness, like a filiform bougie.

With the foregoing conditions of blood volume, general weakness, and rapid pulse, one is not surprised at the low blood pressure characteristic of pellagra. There are exceptions to this, and one is found in the maniacal attacks in insane pellagrins, in which, as Antonini has pointed out, there is a marked rise in the blood pressure. Siler, for instance, using the Stanton instrument on insane pellagrins, found an average pressure of 146 millimeters. Drewry, on the other hand, in 21 cases found it to average 112 millimeters. I have found it as low as 85 millimeters in several female pellagrins, and only once in a woman, and that between attacks, was it as high as 150 millimeters. The average in both sexes ranges around 115 millimeters. There exists here somewhat a similar relation between pulse rate and blood pressure that Hare has pointed out in pneumonia, except, where pneumonia is acute and its duration counted by days, pellagra is chronic and counted by years. As the pulse in pellagra rises, the blood pressure falls; and the greater the pulse rise, the lower the pressure fall. With a pulse of 130 we would expect a pressure of less than 100, continually decreasing toward death. The relation of pulse and pressure, therefore, forms an important prognostic sign.

Sambon examined fresh and stained smears of blood of more than sixty typical cases of pellagra, but was "unable to find any parasite, either protozoan or metazoan, that might account for the disease." Low had the same experience, but further searched for spirochetæ and filariæ, and always with negative results. The study of the bacteriology of the blood has yielded no results of importance. Tizzoni reported the discovery of an organism in the blood, but this has not been confirmed in any degree. Lavinder

has investigated Tizzoni's method, used his technic, planted blood on different culture media, and injected it into different animals, and all with **absolutely negative results.** Hyde's commission also attempted blood cultures, with negative results in all cases. Bass reported 8 out of 12 cases positive to the Wasserman reaction. Howard Fox tested 30 cases by the method of Noguchi, and found 2 cases with a reaction of moderate intensity, and in 5 cases the reaction was only weakly positive. In the light of present researches, pellagra is not a disease in which, even when the reaction occurs, the Wasserman reaction or Noguchi's modification of it is at all strongly positive.

The pellagrous poison has no selective action on the vessels. At times in old pellagrins the arteries are sclerosed, but this is an incident of age and other conditions, and is not produced by pellagra. The heart shows tissue changes that are more characteristic of the disease. The heart is usually atrophied and smaller than normal, more rarely hypertrophied, and occasionally it is dry and friable, the musculature breaking easily under pressure. The characteristic pigmentation of pellagra is present in the cardiac fibers, producing the brown atrophy or brown induration of the myocardial structure. Barden found these pigment granules grouped around the nuclei. Fatty degeneration occurs, but not nearly as commonly as the pigmentation. The interstitial fibrous tissue undergoes development and involves the muscle fibers, and a true myocarditis may occur. Pellagra, by increasing the pulse rate, overworks the heart, and a myocarditis is natural. Valvular lesions in pellagrins are not due to the disease, but are rather complications.

LUNGS.

Pellagra seems to have no direct action on the lungs. Tuberculosis is the most frequent pulmonary complication, but there is no doubt that many of these cases of tuberculosis complicating pellagra are the result of the arousal of a latent tubercular infection from the lowered resistance of the tissues due to the pellagrous toxemia. Tuberculosis in pellagrins is more common in asylums and institutions where confinement indoors is the rule. It is far more rare among pellagrins living in the country districts at home. The rural occurrence of pellagra accounts to a degree for the rarity of pulmonary tuberculosis in pellagrins.

Strambio first called attention to the presence of hydrothorax at autopsy. This transudation of fluid into the pleural cavity probably occurs late in the disease, and in the days just before death, due to the cardiac exhaustion and the embarrassment of the pulmonary circulation. The fluid is clear and the pleural surfaces smooth. Edema and hyperemia of the lungs is a common condition at autopsy. The increased respiration just before death is related to the hydrothorax. Early in the disease respirations are normal, and they are increased to any degree only when fever accompanies the attack, or extreme nervousness is present.

TEMPERATURE.

The older Italian writers considered pellagra a disease without fever. The lack of a clinical thermometer had much to do with their error. Fever in pellagra occupies a secondary position among the symptoms of the disease. We do not lay such stress on the temperature here as we do on the temperature in typhoid for example, where fever is a primary symptom; nor even as much stress as on the temperature in tuberculosis, where it is prognostic of the activity of the tubercular infection. The temperature in pellagra is more nearly related in importance to the temperature in syphilis as a symptom of the disease, from which we may in a measure derive an idea as to the gravity of the attack, and also some idea of immediate prognosis. In pellagra we do not diagnose the disease from the temperature, just as we do not diagnose syphilis from the temperature.

An individual may have pellagra without any fever during the whole of the attack. Sandwith, from a study of 158 of the Egyptian cases, found only 1 of this number with fever, and that one a fatal case with a temperature of only 100°. This almost absolute absence of fever is not nearly so characteristic of the cases seen in America. Out of one series of 50 cases studied by Tucker, the temperature was normal in 21, elevated in 25, and below normal in 4. This presence of fever at some time during the progress of the disease is characteristic of the American cases. It is true, the mild cases have a low fever, rising usually not over 100°, but I find a temperature even in these is not uncommon, especially during the height of the stomatitis and diarrhea, and at intervals for two or three days as high as 101° or 102°. On the other hand,

it is to be remembered that a case may continue during the entire course without any rise in temperature; and, on the other hand, there may be not only no fever, but the temperature may be subnormal, running as low as 96°, and rare cases have been reported with the temperature as low as 92°.

Fever is more apt to be present during the attack and during the third stage of the disease. In the majority of cases a rise in the temperature means an increase in the gravity of the attack, and the higher the fever the more serious the condition of the pellagrin. A decrease in the temperature indicates an improvement in the condition of the patient and a recession of the attack. Fever is more apt to be present in the second stage than in the first, and in the third than in the second. The temperature may be not over 100° until a short time before death, and may continue to rise in the last days and reach 105°, rarely 106°, and occasional higher temperatures have been reported. By far the greater majority of American cases terminating in death are febrile in the last days. The fever is irregular, though it usually shows an evening rise. This is by no means constant, and it may intermit irregularly. In the acute cases the fever is remittent in type, lower in the morning and higher in the evening. The pulse and temperature in pellagra are not closely related. The pellagrous toxin affects the pulse far more than it affects the temperature curve, and there is no disease in which the pulse rate and temperature curve are more independent of each other. The increased pulse rate is a primary effect, and the temperature more incidental. Weakness, emaciation, anemia, and loss of blood volume are factors that tend to produce the pellagrous temperature. Generally a high or continued temperature makes a bad prognosis.

BONES.

There are no special changes in the osseous system in the majority of cases. Lombroso found in a number of cases that the ribs were brittle and broke easily, and occasionally other bones seem more fragile than normal. On the other hand, cases are reported with fractures of the long bones, with the formation of the ordinary callus, and rapid healing and recovery. Strambio noted the sternum and ribs presented an unusually bright-red color at autopsy. He also found a softening in some bones somewhat

analogous to the changes wrought by osteomalacia, but this is probably a nutritional change due to the inability of the system to furnish food to the bones and the withdrawal of the earthy constituents. Lombroso thought the brittleness of some of the bones depended on the eccentric external atrophy of the hard bone and the hypertrophy and activity of the medullary substance. This process produces thinning of the outer portion of the bone, with strain due to pressure from within. In the medullary substance occur at times cells containing red corpuscles and variously pigmented. Further studies are needed on the bones, and such studies would doubtless show that pellagra has no special selective action on the bones as it has on the cord, but rather affects them secondarily, due to the enormity of the nutritional disturbance suffered by the rest of the system. The bones are harder, being part mineral, and therefore suffer least.

WEIGHT.

Loss in weight is one of the most constant symptoms in pellagra. Omitting the dermatosis, there is probably no one symptom always present in every case of pellagra, but there is hardly a more frequent symptom than loss in weight. It is as valuable as it is constant, especially as it gives one an exact idea as to the upward or downward progress of the patient. The information from a pair of scales is worth much of lesser wisdom in a case of pellagra. There is no uncertainty here. If the pellagrin is improving, he is gaining weight; if he is not improving, he is losing weight. At the pellagrosario at Rovereto out of 383 patients treated during the years 1905 to 1907 inclusive, 375 pellagrins gained an average of 12.8 pounds during their stay and treatment, and 8 pellagrins lost an average of 5.5 pounds. These figures include both adults and girls and boys. I investigated this point at the pellagrosario at Inzago, where only boys and girls are treated. Forty boys gained during their stay of a month to five months an average of 6.2 pounds; the smallest gain was 2.2 pounds and the largest 14.7. Following an attack of a disease with so great a wasting power as pellagra, such a gain seems woefully insufficient. The gain would probably have been greater recovering from some disease other than pellagra. As compared with the American cases, the important fact is that these Italian cases are mild and that there is a gain in weight. On the contrary, these

boys averaged under size and under weight at best, and the ever present hookworm probably infected many of them.

Sandwith believes there is always loss of flesh during the attack. My own experience agrees with this as to the American cases.

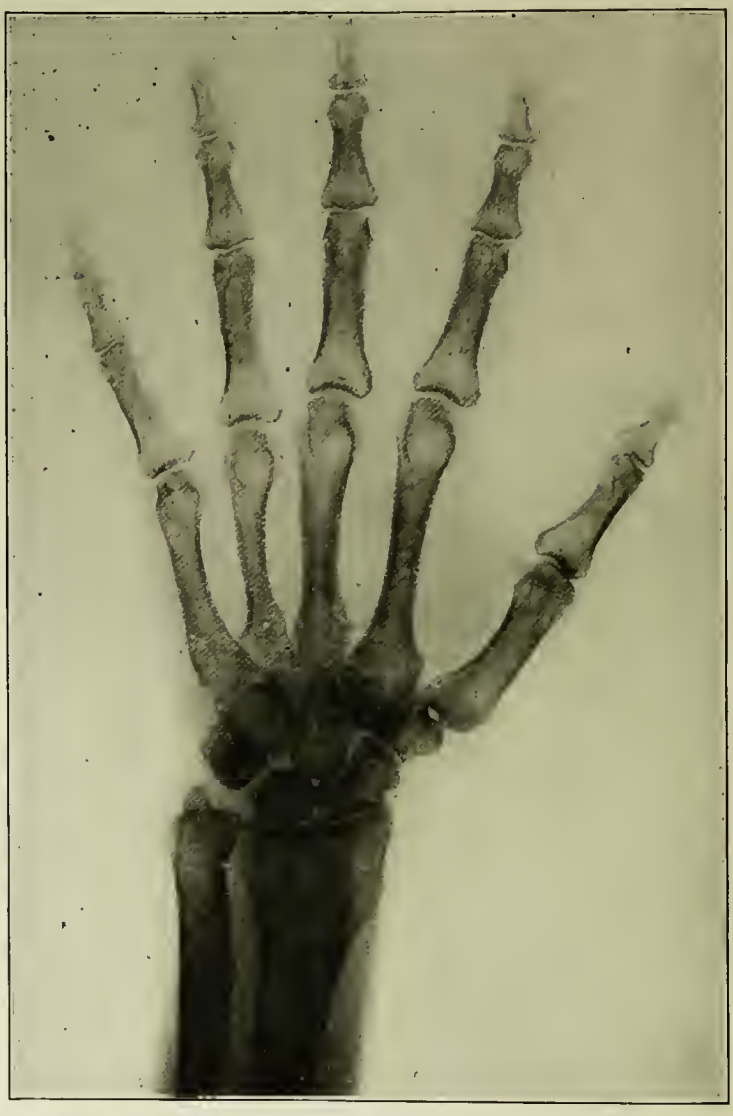


Fig. 59.—An x-ray illustration of the left hand of a female pellagrin, aged 36 years. Note the rarification at the ends of the bones.

Out of 156 cases, 19 left with weight the same as on entrance, 101 gained an average of 5.4 pounds, which means that two-thirds of these cases improved under treatment. Thirty-six lost weight, and in a fatal case 19 pounds were lost before death. After an

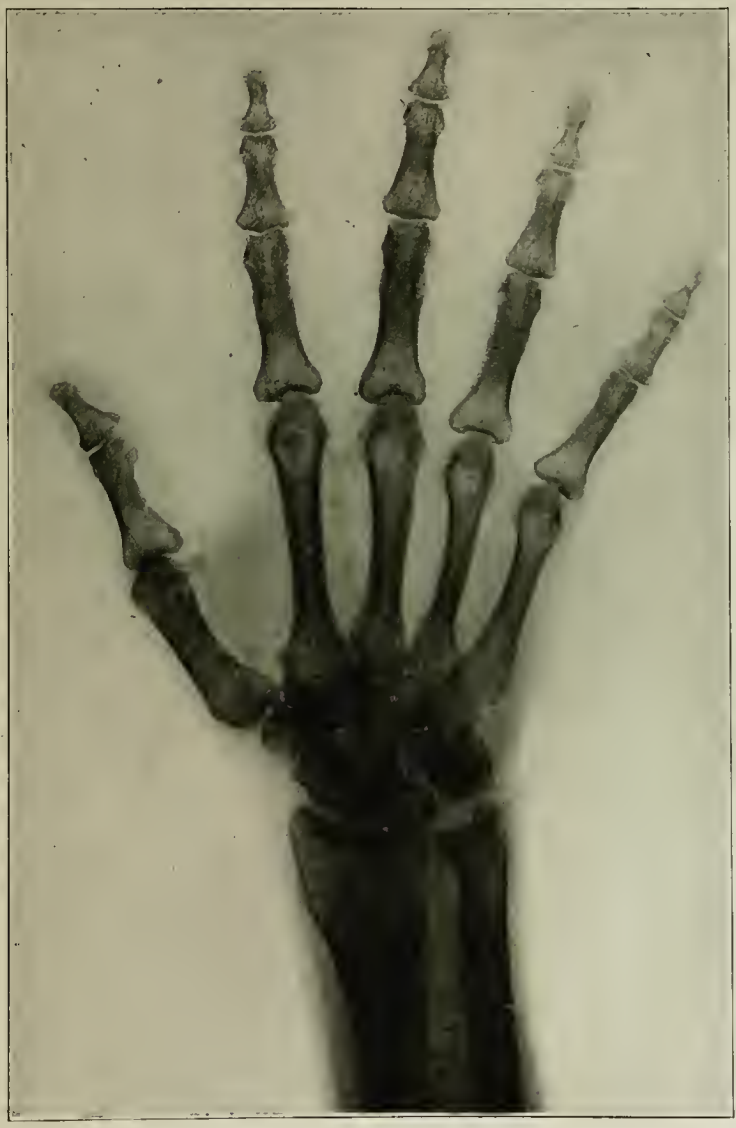


Fig. 60.—Same case as Fig. 59. An x-ray illustration of the right hand, with similar rarification at the ends of the bones.

attack boys and girls gain out of all proportion to adults. The milder an attack, the less the loss in weight. As a chronic case progresses, more and more weight is lost at each annual attack, and proportionately less regained. In the more severe attacks accompanied by fever the loss in weight is very rapid. It is not rare for from 10 to 40 pounds to be lost in a month, and after an attack for a gain of an equal amount to take place in a slightly

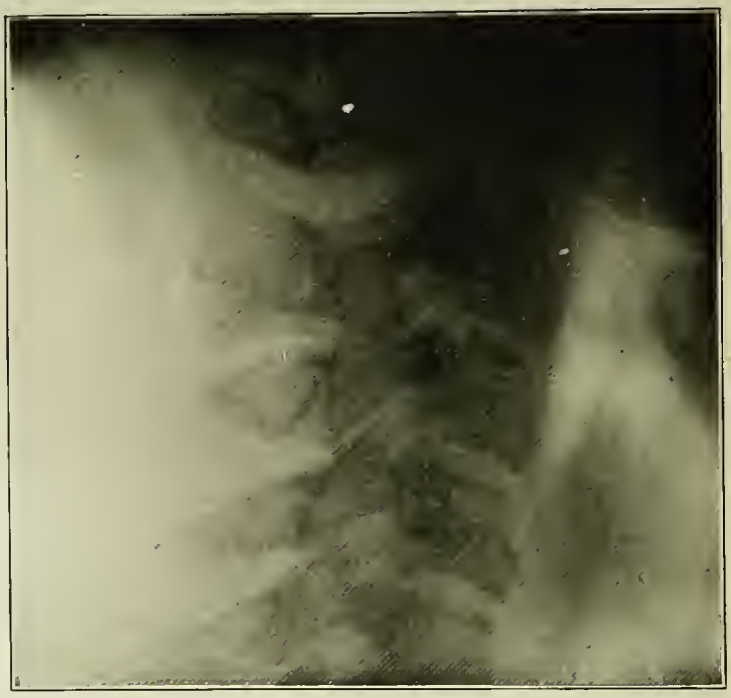


Fig. 61.—Same case as shown in Fig. 60. An x-ray illustration of the cervical region. The bones are practically normal.

longer time. The weight is lost faster during the attack than it is regained after the attack. It is a sign of gravity if weight continues to be lost during the period of recession following an attack. If this continues, the patient is passing into the subchronic or cachectic form, and the outlook is bad. I had one striking experience of this kind with a case in which 16 pounds were lost during the attack, and emaciation continued after the patient was apparently over the attack. Death occurred with a weight of 98 pounds, and a total loss from the beginning of the disease of 42

pounds. Elrod's case gained 48 pounds in three months. Tucker found loss of weight in 52 out of 54 cases, and the other 2 were mild and showed no loss. Zeller reports a case with a loss of 80 pounds, and Tucker one with a loss of 75 pounds.

GENITO-URINARY SYSTEM.

Urine.

The three characteristics of pellagrous urine are (1) a decrease in the twenty-four-hour quantity, (2) a decrease in the acidity, and (3) a decrease in the specific gravity. These changes are not constant, and are not to be expected in each case; indeed, the urine is frequently normal in all details. The more severe or the more advanced the case, the more do these characteristics tend to appear. The analysis of the urine of two female pellagrins gives a fair idea of its condition:

	1.	2.
Quantity in 24 hours	20 ounces (600 cc.)	35 ounces (1,050 cc.)
Reaction	Faintly acid	Faintly acid
Color	Clear, amber	Clear, amber
Specific gravity	1.015	1.005
Albumen	None	None
Sugar	None	None
Indican	Present	None
Microscopical	Great numbers epithelial and pus cells, mucus, triple phosphates, and amorphous urates.	No pus cells, a few blood cells and epithelial cells.

Harris reports two cases with a quantitive estimate of the urea and inorganic constituents. The first is a female, aged 46 years; urine, 690 cubic centimeters in twenty-four hours; acid reaction; specific gravity, 1.015; no sugar; trace of albumen; urea, 16.32 grams; phosphates, 6.63 grams; chlorides, 11.48 grams; microscope shows a few pus cells, but no casts. The second case is a female, aged 54; urine, 1,375 cubic centimeters in twenty-four hours; acid, and with a specific gravity of 1.004; no albumen or sugar; urea, 11.60 grams; phosphates, 2.75 grams; chlorides, 12.55 grams; moderate amount of indican and skatol; Ehrlich reaction moderate; microscope shows nothing unusual.

All these facts in regard to the urine of pellagrins can best

be shown by constructing a table of averages showing the average condition and amount of normal constituents in the urine of healthy individuals as compared with the urine of pellagrins. Practically every condition which influences the body influences the urine, and, therefore, the comparison between these tables is subject to the widest variation:

	Normal individuals.	Pellagrins.
Amount in 24 hours	50 ounces (1,500 cc.)	33 to 35 ounces (1,000 cc.)
Color	Clear, yellow, or red	Yellow
Specific gravity	1.020	1.012 to 1.015
Reaction	Acid	Faintly acid to alkaline
Albumen	None	Rarely present
Sugar	None	None
Indican	None	Very common
Urea	About 1 ounce (30 to 40 grams)	10 to 18 grams
Sodium chlorid	185 grains (12 grams)	12 to 15 grams
Phosphoric acid (phosphates)	2 to 6 grams	1 to 6 grams
Sulphuric acid (sulphates)	2 grams	1 gram
Oxalates	10 milligrams	26 grams
Uric acid	0.2 to 1.4 grams	44 grams
Microscopical	No casts	Hyaline and granular occasionally

These figures on the urine in pellagra are chiefly from work done in the laboratory of Professor Antonini and reported in the record of the Fourth Italian Congress on Pellagra. From the Italian reports it appears that indican is more common in the urine of American pellagrins than in the Italian, but this is probably explained by the fact that the Americans are far greater meat eaters than the vegetable- and fruit-eating Italians. Occasionally in the winter the urine of pellagrins has a specific gravity over 1.020, which, however, decreases again with the onset of the spring attack. In one of these cases in January the urine was 1.028, acid, with large amount of albumen. Alkaline urine has been considered an evil omen, but this is not true. I have seen acute pellagra rapidly fatal, with acid urine throughout its whole course. Sandwith found only 3 alkaline urines out of 168 cases. Tucker reported 3 cases with a specific gravity respectively of 1.031, 1.032, and 1.040. Albuminuria is relatively rare, but it is more often

seen than a typical nephritis with casts. Painful urination is often present in advanced and senile cases. The pellagrous odor so characteristic of the feces in advanced cases is not noticed in the urine. Incontinence of urine may occur toward the last, and the secretion of urine is uninterrupted until death. In nephritis complicating pellagra the ordinary edema is present, but it is not so severe as in nephritis without pellagra. (Procopiu.) This is probably due to the emaciation and loss of flesh. Procopiu found the diazo reaction present in 16 and absent in 32 cases tested.

The kidneys may show no change, but as a rule they are either atrophied, present fatty degeneration, or the tissue changes typical of the different forms of nephritis. They are nearly always smaller than normal. The fatty degeneration may be limited to the tubules. Evidence of the involvement of the glomeruli is rare. There is no change in the adrenals. Bravetta found congestion of the parenchyma of the kidney, increase in the connective tissue, with a diffuse pigmentation.

Sexual Organs and Functions.

The sexual function is dependent in a large degree on physical strength. Certain diseases—as, for instance, tuberculosis—may in some individuals increase the sexual appetite. Pellagra diminishes the physical force, lowers the reserve power, has no exciting influence on the sexual system, and its tendency, therefore, is toward a diminution of the exercise of the sexual power. This influence is not so marked in the early stages, when the strength is greater, but, with the constant inroads of the disease, the generative powers diminish, but even in the early stages the sexual power may be completely lost. Male pellagrins rarely have night emissions, and matters of sex do not concern their minds. The testicles show no characteristic change. At times slight atrophy is present, but this is rather a part of the systemic emaciation.

Pellagra influences the menstrual period. In Italy, as a rule, the menses in female pellagrins are regular, but this is not the case in America. Out of 28 cases in one series, only 1 menstruated regularly, and she was the mother of six children and 44 years old. The other 27 varied from amenorrhea for one to three months to absence of the menses for six to eight months. This is probably best, as it conserves what strength there is in the already anemic and oligemic patient. On the other hand, metrorrhagia

may occur lasting several days, ceasing, and then reappearing without warning. This metrorrhagia is not only exhausting, but it may be painful. Leucorrhea and painful urination occur. The vaginitis has been discussed in the chapter on the Skin (page 132). The breasts atrophy as a part of the process of the general loss of flesh.

Abortions occur in about 20 percent of cases, although a pellagrous female may give birth to a healthy child. Such a confinement is apt to be followed by complications, and especially by post-partum hemorrhage. A pregnancy may relight a latent pellagra, with a rapid onset of a serious attack. Pellagrins should not marry, and pregnancy should be avoided, as it but hastens death in the already disease-shadowed woman. Pellagra may remain latent until after confinement, and then develop during the expected convalescence.

Inflammatory conditions of the vagina, uterus, and diseased states of the ovaries and tubes are more frequent in pellagrins. Leucorrhea adds to the inflammation of the labiæ. Just as there often occurs in the alimentary tract a rectitis, colitis, and enteritis, so in the female genital tract, especially during the attack, there may be found a vulvo-vaginitis, erosion of the cervix, inflamed cervical canal, and an endometritis. On the other hand, there may be a simple vaginitis with leucorrhea. Ovarian neuralgia, ovarian cysts, uterine fibroma, and the various displacements of the uterus are found frequently in pellagrins, but they are rather to be considered as complications, whereas the vaginitis, endometritis, and leucorrhea, with menstrual irregularities, are directly due to pellagra.

Complaints, especially in women, are lodged against the sexual organs. The female pellagrin becomes conscious of her pelvis after the manner of a sexual neurasthenic. I have seen several cases operated on for a supposed gynecological condition when in reality the woman was pellagrous, and her genital complaint was what Eleanor Saunders well called an "incidental" in the course of the disease, and, as she well adds, "the majority of such patients should be treated not as having a primary organic pelvic disease, but as suffering from functional or symptomatic disorders." The gynecologist and the surgeon may be thrown off their guard by the genital complaints of pellagrins. A history of loss of flesh, emaciation, diarrhea, recurring vernal lassitude, ought to raise the

question of pellagra before operation for anything is decided upon. Operations on pellagrins do not offer encouragement, and only a most severe reason should permit surgical procedures.

ORGANS OF SPECIAL SENSE.

Eye.

There is no condition of the eyes pathognomonic of or peculiar to pellagra. On the contrary, normal eyes in well-developed cases of pellagra are rare, but the chief reason for these abnormalities lies in the systemic asthenia, the lowered nerve power, and the effect of the circulating toxins of pellagra on the nervous system and the ocular apparatus. Eye weakness is present, and the ocular muscles and visual powers become fatigued rapidly, but all this is but a localized example of a systemic nerve and muscular debility. Sir William Gowers defines the eye as an outpost of the nervous system, and well says that it "presents the most delicate example in the body of the relation of nutrition to the nerves." The state of the eye depends on the nutritional state of the nerves which supply its various parts, and in pellagra this nutritional state is strikingly lowered. Therefore, the eye changes in pellagra, while technically interesting to the oculist, are part of the larger toxic and systemic process influencing the whole body.

F. P. Calhoun, of Atlanta, in his investigations on the eye in hookworm disease, finds somewhat similar conditions as are present in pellagra. He has seen 10 cases of cataracts depending on hookworm infection, and in 1 of these which he showed me and in some others the hookworm infection was mild, and the cataract in his opinion was due to the effects of the toxins eliminated by the worms. As shown both by Fabricius and Procopiu, cataracts are of unusual frequency among pellagrins, even pellagrous children developing them in the form of milky cataracts. Welton, in his investigations in Peoria, refers to the fact that "early forming cataracts are frequently noted," and Tucker found cataracts in 3 out of 45 cases; Whaley, in South Carolina, found cataracts in 5 and cloudy lens in 1 out of 35 pellagrins. This tendency to cataract formation both in hookworm disease and in pellagra is due to the metabolic degeneracy of the entire system, the altered and lowered nutrition of the lens, as determined by the persistence of the hookworm and the pellagra poisons.

The severity of the eye symptoms runs parallel with the severity of the general manifestations of the disease, and the findings of marked eye changes add to the gravity of the prognosis in pellagra and indicate in a large percentage of cases an early fatal termination. (Welton.) Among the eye changes depending on the general weakness are diplopia, or double vision; hemeralopia, or night blindness; photophobia, or fear of light; mydriasis, either unilateral or bilateral, but more often affecting the right eye when unilateral; ptosis, lachrymation, and conjunctivitis. Other changes are shallowness of the anterior chamber, paralysis of one or more muscles, sluggish pupillary reflex, atrophy or redness of the papilla, sclerosis of the retinal vessels, dilatation of the retinal veins, with a grayish or yellow cloudiness of the retina. Whaley found a dilatation of the retinal veins very common, and Calhoun has noticed the same condition in hookworm disease. Ulcers of the cornea, retinitis, choroiditis, inflammation of the optic nerve, and a combined retinochoroiditis occur, but are more rare than the first mentioned changes. The studies on the eye thus far have been made on cases rather far advanced and on asylum cases, and in both the nerve changes are apt to be pronounced. A study of the eyes of the mild and recent cases and a comparison with the ocular studies in asylum cases would add to our knowledge of the effect of pellagra on the eye.

Ears, Taste, Touch, Smell.

Pellagra has very little effect on hearing, and in far the majority of pellagrins hearing is normal. Tucker found it diminished in 5 out of 46 cases, and Green found it impaired in 8 out of 60 insane pellagrins. In some cases, when the ability to hear appears slightly diminished, it will be found due to the condition of apathy and silence rather than to lack of ability to understand when spoken to. It is evident also that with a series of organic changes in the brain and cord, emaciation, and nerve exhaustion, the other special senses, like the hearing, would tend to be dulled and less acute than in the vividly healthy.

Taste and smell are in the majority of cases normal, and, when affected, are slightly diminished. In mentally sound pellagrins I have been unable to find any marked change in either sense. In certain sections of Italy the persistent salty or briny taste is complained of, and I have found this in a negro female in Georgia.

Green found it impaired in 2 of his 60 cases, and Tucker thought it was diminished in 21 out of 46 and "coppery" in 1 case. Smell was lessened in 9 of Green's cases, and in 6 of Tucker's 44 cases.

The disturbances of sensation in regard to itching, pruritus, formication, and burnings have been previously discussed in the chapter on the Skin (page 121). The special sensation of touch is not affected to the extent that it is in such diseases as hysteria and locomotor ataxia. With the esthesiometer the distance between the points is increased in a number of cases, but not to any marked degree. On touching objects, change in sensation is often noted—the pellagrin complains that the objects feel "far away," and seems unable to relate the sensation of the object in his mental processes. The sensation to temperature is more often impaired than the mere sense of touch. In about 10 percent of cases this sensation of heat is lowered, and at times in the lower extremities may be so impaired as to remind one of the changes in syringomyelia. Anesthesia to cold may prevail in localized areas and hyperesthesia to heat, and vice versa. The systemic sensibility to heat and cold varies, and, as a rule, excessive heat is avoided, but I remember one pellagrin who sat in front of the fire constantly and seemed always more comfortable in the presence of such heat.

CHAPTER VIII.

DIAGNOSIS AND PROGNOSIS.

DIAGNOSIS.

The fundamental element in the diagnosis is to remember that pellagra is a definite disease, an exact morbid proeess, and separated from other diseases by well-marked symptoms. The longer one studies pellagra, the clearer are its symptoms and the more sharply it is defined as an entity. A diagnosis is made independently of any idea of its eausation or of any theory regarding the etiology. In the present state of our knowledge, etiology and diagnosis are not to be considered together. If one attempts to relate his diagnosis to any pet theory he may have formed as to etiology, he is apt to find his theory influencing his diagnosis, and especially in the more diffieult cases. The diagnosis depends on the symptoms presented and not on any theory as to cause.

The diagnosis is made by the observation of the external clinical symptoms, the history, and the present condition of the patient, and it does not depend on laboratory findings to an important degree. It involves exact clinical observation, and in the present state of our knowledge the miscroscope is of little avail. It is true, in very obscure eases the increase in the lymphocytes in the blood may afford slight evidenee, but one is not justified in making a diagnosis of pellagra on either the changes in the blood or the urine. In pulmonary tuberculosis the presence of the tubercle bacillus in the sputum clinches the diagnosis, in diphtheria the finding of the baeillus of Klebs-Löffler in the culture does the same, but in pellagra thus far there is no bacterium that aids in diagnosis, much less permits a positive diagnosis. The dermatosis clinches the diagnosis of a suspected pellagra just as the finding of the malarial parasite in the blood confirms a suspicion of malaria. Observation with the naked eye is of service.

If in the future the history of pellagra in Ameriea is what it has been in Italy, Egypt, and Roumania, the type will become

less acute and less severe, the course more chronic, and the damage wrought by the single attack far less because it will be more mild in character. It will probably increase among children, and in them the dermatosis be so temporary and slight as to resemble more the ordinary sunburn than a decisive diagnostic element in a very chronic disease. The acute and grave cases, rapidly progressive, are easier of diagnosis than the more chronic and mild forms. In these milder cases associated infections are present, and, as has been stated, the symptoms of pellagra may interlock with the symptoms of hookworm, for example; and, while the latter are easy to determine, the superimposed pellagra, especially in the latent period, may be difficult, if not impossible. The symptoms of pellagra are thus obscured by its very complications. Outside the dermatosis, which occurs during the attacks, the diagnosis is based not on one symptom, but on a group of symptoms, on the syndrome as a whole, and, with a suspicion of any associated infection, it is well first to take into account what conditions and symptoms are due to the associated infection, and then one is in a surer position to consider the remaining symptoms. One diagnosis at a time, in one suspected of pellagra and a complicating disease, is a good rule. Then the real essence of a diagnosis becomes evident—that pellagra is a disease diagnosed not on one symptom, but on the association of a group of symptoms. The tongue may be inflamed, and, considered by itself, would constitute a glossitis; but an inflamed tongue, with a diarrhea, a peculiar bilaterally symmetrical dermatitis, followed by a rough skin, a cedar-wood colored pigment, becomes a pellagra, which has as one of its symptoms a glossitis.

Another factor in diagnosis is the fact that pellagra is not always active. It hides itself in the grass as a snake in its times of latency, and then reappears with the fury of fire in its attack. The attack may be very mild and short, and then the period of latency and hiding is long. Diagnosis is possible in the period of latency as well as in the period of activity, and the resting time presents a group of pellagrous symptoms, together with the history, which permit a diagnosis. One should be as familiar with the symptoms of the latent period or intermission as he is with the classic symptoms of an attack.

The diagnosis varies with the time of the disease, the severity, and the number of attacks. It is evident that if there have been

repeated attaeks, with a persistent pigmentation on the hands, roughness on the elbows, emaeiation, slowness of the mental proeesses, the diagnosis is very mueh more easy than if only one or two mild attaeks have oeeurred, and between them the patient has appeared about as well as usual. Pellagra appears to the physieian for diagnosis in four different ways, and the symptoms on which a diagnosis is made differ in eaeh of the four ways. These four appearanees are as follows:

1. Pellagra suspeeted by symptoms presented during onset.
2. Diagnosis by symptoms presented during an attaek.
3. Diagnosis by symptoms presented in the intermission between attaeks.
4. Diagnosis by symptoms presented in the type pellagra sine exanthemata, or pellagra without the eruption.

1. Pellagra Suspected During Onset and Before the Dermatitis.—Next to aeeuraey in diagnosis is the neeessity for an early diagnosis. The sooner a positive diagnosis is made, the more quickly ean treatment begin, and the better the ehanees for improvement. Pellagra may be so mild that the patient is not aware of any prodromal period, and during the first or seeond attaeks no need for eonsultation with a physieian is felt. He is a little weak or languid, but nothing more. On the other hand, even in the severe eases, a physieian is not eonsulted until the attaek is at its height or great weakness is present. The period of onset may last several weeks, and the question arises on what symptoms may the physieian with reason suspeet an oneoming pellagra. A positive diagnosis at this time is uneertain, and in far the majority of eases impossible; but suspieion in diagnosis is the mother of attention, and generates eareful examination for eonfirming evidenee.

The period of onset may last from a few days to three months in extreme eases before the dermatitis appears. Diarrhea without apparent eause may appear, and the tongue may be red on the tip and margins. Uneasy sensation in the abdomen, rumblings in the intestines in one previously healthy, together with the diarrhea, not a dysentery, are suspieious. Along with these, insomnia without external eause, exaggerated reflexes and espeeially knee jerks, loss of energy, a eontinued sense of lassitude, add evidenee for a suspieion of pellagra. Loss of flesh in the last few days or weeks, lowered specific gravity of the urine, and an inerease in the small lymphoeytes of the blood are important diagnostie points.

A decreased acidity or total absence of free hydrochloric acid in the gastric contents in connection with the increased reflexes, the decreased specific gravity of the urine, the fact that the patient lives in a rural environment, and that the season is the spring time or early summer, would involve the necessity for an examination of the hands, elbows, and skin of the entire body. The physician should see the patient every second or third day for the confirmation of his suspicion by the appearance of bilaterally symmetrical dermatosis, or the error of his suspicion by the failure of such a dermatosis to appear. The physician here is in the same attitude of waiting as when he has a case of suspected syphilis and waits, as the elder Gross of Philadelphia advised, for the appearance of the syphilitic eruption. If this case of suspected pellagra is in an endemic pellagrous locality, and several cases have already developed in the neighborhood, it bears careful watching.

2. Diagnosis During the Attack.—A diagnosis of pellagra is made with ample evidence when the dermatosis appears. The appearance, localization, and development have been described in the chapter on the Skin (page 121). To summarize for purpose of diagnosis, it appears as the first symptom of pellagra in many cases, but in most cases follows digestive and nervous disturbances; it is bilaterally symmetrical, appearing always on the back of the hands, and it may extend to the elbows, face, neck, sternum, feet, and rarely to the trunk and thighs. Areas of roughness develop usually on the elbows and more rarely on the knees, forehead, forearms, and legs; the dermatitis is reddish brown, like that of a dark-colored piece of red cedar wood. The dermatitis is followed by a persistent scaling, and it may occur several times in one season. After several attacks the back of the hands become permanently pigmented and rough, and the elbows become dry, rough, and divided into small rhomboidal areas.

The skin condition is to be differentiated from four other skin lesions—sunburn, alcoholic dermatosis, eczema, and erythema multiforme. In sunburn there is always a history of an unusual exposure to the sun, followed that night or the next day by the changes in the pigmentation of that skin area directly sun-exposed —as a rule, the back of the neck, the back of the hands, and the face. There are no constitutional symptoms, the patient knows the cause, the roughness on the elbows is lacking, the eruption heals quickly, and is not followed by a continual scaling and shedding

of the skin. The alcoholic dermatosis appears in chronic alcoholics, with severe constitutional symptoms, the chief of which are an alcoholic neuritis, with pains in the lower extremities, wrists, and foot drop, a nephritis or uremia, and mental symptoms—as unconsciousness or delirium. The dermatosis—or ethylic erythema, as it is sometimes called—has an exfoliation of the epidermis on the back of the hands, a roughness of the elbows and knees, but there is no great **pigmentation** on the back of the hands. The alcoholic history is present; the neuritis, the wrist drop, and the hands heal rapidly.

The pellagrous dermatosis is to be distinguished from a dry, scaly eczema and an acute erythematous eczema. Itching is apt to be present in both of these, without a general constitutional disturbance, diarrhea, or sore mouth, and the skin lesions are not typically bilaterally symmetrical. In the erythematous form, too, slight irregularities or elevations of a pin-point character often appear on the reddened area. These are absent in pellagra. In erythema multiforme there is no scaling, the constitutional disturbance is slight or absent, and the spots have a bright-red areola. The eruption here is symmetrical, but the spots either in the papular or bullous form are discrete and circumscribed, and cover a larger area than the ordinary pellagrous dermatitis.

There may develop in chronic septicemia, alcoholism, or uremia a sore mouth, red tongue, raw and painful, and a stomatitis which involves the oral cavity. I have seen this condition once in a woman following an operation for appendicitis, with abscess and septicemia, and also in a case of acute uremia, and in a man with general alcoholic poisoning. Chronic septic conditions, alcoholism, or uremia cause mouth conditions closely simulating pellagra, but they are similar to pellagra only as regarding the mouth, and even here the tongue is more apt to be coated in the center, whereas in pellagra it is without a coat. The history of the case, anemia, acute nephritis, edema, alcoholism, septic foci and pus formation, absence of diarrhea and the dermatosis, serve to distinguish all these from pellagra.

After the dermatosis is diagnosed as pellagrous, and the sore mouth and coatless tongue accompany it, whatever associated symptoms of a pellagrous character exist alongside assist in the confirmation of the diagnosis. The diarrhea associated with the increased reflexes, the peculiar odor of the feces, the decreased gastric acidity,

nausea, sensations of weight in the epigastrium, aversion to food or increased desire for food, gas in the intestines, associated with the dermatitis and the stomatitis, constitute a picture which permits of no doubt. The diarrhea may in the South cause one to think of sprue, especially as in sprue there is a sore mouth, but here the movements are whitish in color, lack the pellagrous odor, and the skin and nervous symptoms of pellagra are absent. The changes in the urine—as lessened acidity, specific gravity, and decreased twenty-four-hour secretion—the increase of small lymphocytes in the blood, the low grade secondary anemia, afford some further evidence.

Among the general symptoms are the loss in weight, the spring or summer season, the rural environment, the retardation of the mental processes, the lack of inclination or ability to do work of ordinary character, the tendency to silence and the look on the dark side of life, and the desire for rest and inertia. The appearance is sometimes helpful. Just as one sometimes involuntarily thinks of hookworm disease when he is suddenly brought face to face with a patient severely infected, so the aged appearance, the stooped shoulders and bent gait, the thin angular face, the wrinkled and drawn forehead, the bronze or pinkish tint to the face, are all in turn characteristic of pellagra. The typical dermatosis, the tongue, mouth, diarrhea, and the increased reflexes, and nervous and mental symptoms, associated in the same patient at the same time, can give no trouble as to the diagnosis. The physician, to diagnose pellagra, must remember that the disease pellagra exists. Then the association of its plain symptoms makes the diagnosis during the attack very easy.

3. The Diagnosis of Pellagra in the Intermission Between Attacks.—In a few cases, preceded by very light attacks, the diagnosis at this time may be exceedingly difficult, but, as a rule, on close observation diagnosis is possible. The snake is in the grass, and, while we may not be able to see all of him at once, we can get glimpses of his head, his tail, or the middle of his body, clear enough to satisfy us that he is present. In the time of intermission what cutaneous, digestive, and nervous symptoms are present, and what general symptoms and points from history can be obtained, when associated together constitute a syndrome—peculiar to the latent time.

What skin symptoms are present between attacks? The three

present in the majority of cases are the unusually pink fingers, the increase in the wrinkles over the first phalangeal joints of the fingers, and the roughness on both elbows. In old cases pigmentation may be found on the back of the hands, and the skin is

Fig. 62.—Pellagrin after recovery from attack. Note contraction of little and ring fingers of left hand, following the severe dermatitis with edema. (Case of Dr. J. O. Elrod, Forsyth, Ga.).

wrinkled, dry, and has fine branny scales which can be seen when looked at closely. The extensor surface of the forearm is often more rough than normal, and the whole hand may be strangely long and thin. Walnut-stained spots or chloasmic spots may remain on

the face or neck, the forehead may be slightly rough or wrinkled, and a pink, drawn face add the final touch to the peculiar pellagrous facies.

The digestive disturbances are wanting at this time, or there may be a complaint that digestion is not as good as formerly, the bowels are relaxed, and every few days several loose movements may occur, whereas the patient was previously constipated. Rumbling and gaseous distention in the intestines may continue. The tongue now is usually coated, though not heavily, and the margins appear very clean. At the tip a few red papillæ may be seen—by themselves meaning nothing, but, in association, the remnant of the former coatless and inflamed tongue of the attack.

What nervous and mental symptoms are present? The general condition of the nervous system is according to the number and severity of the former attacks. In the mild attacks no great change is noticed, and the mind acts with its accustomed vigor. Even here, however, the pellagrin is unable to maintain the expenditure of physical strength over long periods of time, nor is his energy initiative in character—it rather flows with necessity and the routine of the day. He does not object to rest. Occasionally, on close observation, the hands will be found with tremors after slight exertion, and the fingers may tremble when separated and the arm extended. In a more advanced case the knee jerks are exaggerated and often markedly so, tremors and weakness are marked, the legs are unduly unsteady, and the gait more uncertain. The face and eyes are not those of a mentally active person, the pupils are often dilated, speech, while not disturbed, is slow, and few words are spoken. The history of the case differs from that of paresis, the specific gravity of the urine is less, speech disturbance is absent, and at this time the reflexes, with but few exceptions, are markedly increased, and the syphilitic pupil of paresis is absent. The history of the case, circulatory changes, nephritis, neuritis, alcoholic delirium, separate chronic alcoholism from pellagra.

In women living in rural districts complaining of unusual lassitude and weakness for one or several spring seasons, a chronic vaginitis, a leucorrhea, cervical erosions, digestive disturbances, exaggerated reflexes and emaciation, or even with the symptoms of involvement of the genital tract absent, no operation should be considered or advised until pellagra is considered and ruled out as a cause. The same statement applies to this class of patients suf-

fering with gastric and intestinal symptoms. Gall bladder operations on pellagrins neither cure the pellagra nor lengthen the life of the pellagrin.

Fig. 63.—Pellagra in time of intermission. Patient has typical walnut stain on upper lip, and yellow spots on face. Condition after three spring attacks.

4. Diagnosis of Pellagra Without the Eruption, or Pellagra Sine Exanthemata.—It is doubtful whether a patient can have pellagra for a long series of years without any skin symptoms whatsoever. For example, the dermatitis may be absent and the dermotagra present, or the dermotagra present only for a few days

when the digestive and nervous disturbances reach their height. It is true that pellagrins have pellagra without the dermatitis, and suffer a typical spring attack or more than one such attack with the absence of the dermatitis or a marked roughness of the skin.

Fig. 64.—Same case as shown in Fig. 63. Elbow slightly rough; hands appear normal, except on very close examination, when fine branny scales are seen.

In these cases the diagnosis is, of course, more difficult than when the characteristic dermatosis is present, but a diagnosis can be made.

First, other diseases—as chronic dyspepsia, gastritis, amebic

dysentery, neurasthenia, chronic hysterical temperaments, diseases of the gall bladder and intestines—must be considered and ruled out. Then the environment of the patient, history of spring sickness, flurries of diarrhea, sore mouth and coatless tongue, disturbances of digestion and uneasy sensations in the abdomen, absence or marked decrease in the hydrochloric acid of the gastric secretion, will give evidence from the alimentary tract. Nervous and mental changes peculiar to pellagrins, and especially the exaggerated knee jerks, dilated pupils, retardation of ideas, loss of memory, emotional disturbances, will give more evidence. Finally, the presence of the triple changes in the urine—a decrease in the twenty-four-hour amount, the specific gravity, and the acidity—with slight secondary anemia, increase in the small lymphocytes at the expense of the polynuclear cells, serve to confirm or to dismiss our tentative diagnosis. Loss of flesh without other apparent cause is characteristic in this class of cases.

PROGNOSIS.

The prognosis in pellagra depends on the type of the disease with which the patient is affected. In that class known as acute pellagra, characterized by fever, prostration, high pulse, continued diarrhea, the prognosis is, of course, bad. These cases frequently recover from one or more attacks, and even very occasionally have no recurrence of the disease, but, as a rule, the outlook is bad, and the early advent of death may be expected. In the subchronic convalescent form the prognosis is bright, the attacks are mild, improvement is rapid, and permanent recovery is to be expected. In the subchronic cachectic form the progress of the disease is rapid; emaciation, high pulse, nerve symptoms, a more or less chronic diarrhea, make the outlook bad, though, of course, here final dissolution is neither as rapid nor as certain as in the acute forms. In the chronic form the prognosis is fair, and can be called neither good nor bad. Even if the disease is not cured, the patient will probably live for several years, and there is a reasonable hope of marked improvement.

The prognosis varies in different countries, and thus far it has certainly been more grave and the mortality higher in this country than elsewhere. For the nine years from 1901 to 1909 out of 636 insane pellagrins, asylum cases, there were according to War-

noek's report 93 deaths, or a mortality of about 15 percent. Sandwith, treating pellagrins not insane, found out of 437 treated in the years 1895, 1896, and 1897 there were 17 deaths, or a general death rate of 4 percent. These represent asylum and hospital eases in Egypt. Lombroso, quoted by Lavinder, for the year 1883 in Italy, out of 6,025 pellagrins treated in the eivil hospitals, noted 923 deaths; and in 1884 there were treated in these eivil hospitals 6,944 eases, with 780 deaths, or an average mortality for both years of nearly 13 percent. Wollenberg eolleeted a total of 55,029 eases in Italy in the year 1905, with 2,359 deaths, or a total mortality of slightly more than 4 pereent. The mortality in Egypt and Italy is about the same. Babes and Sion are even optimistie of the eases in Roumania, and espeeially of those outside the asylums. I found that Fritz, at Inzago in the provinee of Milan, and Probitzer, at the pellagrosario at Roverето in Austria, will go through a whole year without a death, and more than 90 percent of their cases show improvement. It is rather the exeeption for a death to occur in those who eome to these pellagrosari to be treated, and the death rate in Italy is dependent on the aged pellagrins, the chronie cases who have suffered many years, and the advaneed asylum eases. The progress of pellagra in Ameriea will probably give the same history as to mortality in the near future.

Contrasting these figures and data with the prognosis and mortality so far in Ameriea, it is elearly evident that the disease in this country is of a far more severe nature, more rapidly progressive, and proportionately more fatal. Bass, of New Orleans, has already ealled attention to the faet that the disease is less severe and acute in type in Louisiana than formerly, and it was with difficulty reeently that he was able to find a case with the ordinary manifestations severely marked, whereas in 1908 and 1909 sueh cases were common. Bresadola, in Rovereto, showed me a woman in September, 1911—the worst ease he had. She was up, walking around, and he remarked, indieating how the general type of the cases has lessened in severity, that in 1909, two years previously, this woman was the mildest ease in the hospital. Indeed, Merk stndied the disease in Rovereto, and gathered here the pietures for his great "Atlas on the Skin in Pellagra," and now all these severe eases have ceased to develop in the Tyrol. As before stated, the disease will probably show the same evolution here in America, with an ever-increasing mildness in the individual

cases, a decreased mortality, more cases which present a permanent improvement, and an increase in the length of the cases and a decrease in the severity of the single attack.

The asylum cases in America have had a mortality of between 40 and 60 percent, with an average of about 50 percent. It is true that in the beginning there were a few places, as in Alabama, which showed for one year a higher death rate, and even this average of 50 percent will probably decrease each year. The cases outside the asylums and treated by physicians in general practice have a mortality of about 25 percent, though frequently in different communities the death rate will be lower, and I have found physicians treating 20 cases in a county with only 2 deaths in a year, or a rate of 10 percent. Probably for the year 1912 the rate will not be over 20 percent. In the next five years in the United States the number of cases of pellagra will probably continue to increase, and the death rate will probably continue to decrease.

The question arises as to the prognosis in the individual case. This is grave if the patient has any complications or chronic disease which reduce the strength and resisting power. Here are included surgical operations, frequent pregnancies, hookworm disease, tuberculosis, and syphilis. It is the opinion in Italy and France that alcoholism predisposes to pellagra, and it is borne out in America to a degree. It is certainly true that an alcoholic bears pellagra badly, and in him the disease is usually rapid and the prognosis very grave. In my experience it is equally grave in chronic cigarette smokers, in those confined indoors for long hours, and in those whose purse does not permit change of diet and variations in the articles of nourishment. The prognosis in children is even more favorable than in adults.

The attack in pellagra is often deceptive. The patient may lose 20 to 50 pounds, lapse into unconsciousness, develop fever, pulse of 120, and seem near death, and then gradually improve, and in three months regain the lost weight. The character of the eruption offers no evidence as to the type of the case or its outcome, except in those few cases with the dermatitis so severe as to produce vesicles—the "wet" form—the cases are severe and the prognosis bad from the beginning of the first attack. Fortunately such cases are rarely seen and are decreasing in number. If the pulse rises over 100 with the patient in bed, the attack is severe, and over 120 the patient is in danger as a rule. The same statement applies to

a temperature over 100°, though one sees cases with fever as high as 103° improve and live several years. Continued diarrhea, with rapid loss of flesh, prostration, symptoms of delirium, subsultus tendinum, abolition of reflexes, are precursors of death. Before death the abdomen may become distended from a paresis of the intestines, and cause much discomfort. Contractures of the muscles, changes in the gait, mental decay, spastic conditions, ankle clonus, Babinski reflexes, are signs of organic changes in the cord and brain, and these organic changes are not subject to treatment or marked improvement. Rapid loss of flesh, severe prostration, high temperature, and rapid pulse unite to put the patient on the danger line.

The prognosis is most favorable in proportion to the promptness of the diagnosis, the mildness of the first attack, and the persistence of the treatment. The prognosis is far better in the stage of dyspepsia, or the first degree, less so in the stage of neurasthenia, and hopeless in the stage of cachexia. Any case will live long in proportion to the severity of the injury to the nervous system. Recovery from the dermatitis does not mean the cure of the pellagra. The dermatitis may heal and the patient grow worse. The pulse, temperature, weight, and diarrhea are far better signals to watch and to follow than any evanescent coloring and scaling of the skin. The dermatitis never kills. The one best prognostic sign from month to month is the weight. There can be no mistake in depending on this great mass symptom of the disease. If there is an attack this spring, will there be another next spring? Here the physician is helpless. He does not know. There may never be another attack, or it may recur each spring until death, or, except for a slight lassitude for several spring seasons, a second attack may be delayed for several years. Despair on the part of the physician is as bad as despair on the part of the patient. A vast hope, backed by persistent treatment, brightens the prognosis in every case.

CHAPTER IX.

TREATMENT OF PELLAGRA.

Pellagra does not mean death. Treatment is of avail. Treatment certainly will not cure every case, and death will claim many, but careful medicinal, hygienic, and dietetic measures will give marked improvement in a majority of cases and prolong life. The question then arises as to how the physician knows when a case is cured. From the foregoing pages it is evident that pellagra is a durable disease, recurring annually or at longer periods. Because the pellagrin improves and the evidences of his disease depart is no proof that the pellagra has gone or is cured. Therefore, one can speak correctly of a cure in a given case only when two or more years have elapsed, during which time the patient has shown a constant improvement in health and strength, and there has been no attack or return of noticeable pellagrous symptoms.

When a pellagrin recovers from an attack, it is manifestly incorrect and unwise to speak of a cure. There has been a recovery from a single attack, an improvement in the condition of the patient, but it is too early to even use the word cure. The physician saves himself embarrassment later if there should be a recurrence. It takes time to pronounce a pellagrin cured, and recovery and improvement are strong enough words to use. When the attack recedes and the symptoms depart, the patient can well be said "to be improving and he will recover from this attack." He is not at this time to be referred to as "cured." As a result of treatment, the word **improvement** meets both the present situation and, on the other hand, does not imply that the following autumn or the next spring there may not be a recurrence of the attack. If the improvement is excellent, if the patient gains flesh rapidly, if the diarrhea, weakness, and nervous symptoms recede and strength returns, the patient may be said "to show a marked or radical improvement." If the condition of the pellagrin is such that so great improvement is impossible, and yet, as a result of treatment, he actually is some better, he may be said "to show a

satisfactory improvement." If he shows failure to respond to treatment, or the case rapidly assumes the eachectic form, there is simply "no improvement." No physician is wise enough to prophesy death even in the very severe attacks. He is often surprised at the very marked improvement that follows in cases that seemed near death. Even in the most aggravated eases in the third stage, cacheetie and prostrated, with dissolution apparently at hand, the patient frequently lingers far longer than expeeted.

The first step in the treatment of pellagra is to aseertain whether any other disease is present. As stated before, pellagra is disease enough for any patient to have at one time. Its draining and resistanee-lowering powers inerease the capaeity of any associated infection or disease to do greater damage. Pellagra affords fight enough to test the strength of the patient and the skill of the physieian. Any other discase inereases the danger and lessens the ehanee of improvement from treatment. Pellagra acts as an alarm eloek to awaken a sleeping infection. The pellagrin should be examined for tubereulosis, intestinal parasites, and malaria, and syphilis is not to be forgotten. The feees should be examined for amebæ and espeeially for hookworm ova, and oeeasionally other ova may be found. In the South a latent malaria or hookworm infection is ehiefly to be expeeted an assoeiated infeetion. The treatment for either of these, if present, should be instituted when possible as soon as diseovered, and the treatment of pellagra continued at the same time. The eure of one of these assoeiated infeetions is really a part of the treatment of pellagra, because the pellagrin is benefited. Inereasing the resisting power of the pellagrin is the first step in the treatment of his disease.

There is a distinetion between the treatment of pellagra and the treatment of any of its symptoms. Both require treatment and are closely related, yet the treatment of the dermatitis is not a treatment of the disease. The disease is internal, tissue-seated, silent, unseen, and progressive. The symptoms are external, objective, seen or felt, and reeessive. The symptoms eome and go; the disease may remain. The symptoms improve as they disappear; the disease lessens its aetivities in proportion as its external manifestations disappear. The dropsy from insuffieiency of the mitral valve may disappear, but the insuffieiency remains. The swelling goes, but the leak eontinues. The dermatitis and diarrhea go, but the disease within continues. The treatment is therefore twofold in

character—(1) the treatment of the disease, and (2) the treatment of the symptoms of the disease.

The treatment of pellagra is devoted against the disease itself primarily, and considers its objective symptoms only secondarily. It consists of medicinal, dietetic, and hygienic measures.

MEDICINAL TREATMENT.

There is no drug which cures pellagra. It has no specific. There is one best drug, and that drug is arsenic. It will not cure every case. Many cases will not improve under its use. If they will improve at all from the use of any drug, they will improve by taking arsenic. If no improvement follows its use, then the disease itself, not its symptoms, will not be influenced by any drug. If one takes the physicians in any average county, they will be found to be using a variety of drugs, often as many as twenty different ones, each physician using different ones to a degree, and all directed against one morbid process. It is certain that if it takes twenty, or even ten, drugs to cure or improve a patient, not one of them is of very much service, and all of them together had better be omitted entirely.

Arsenic can well be given in full doses, and pellagrins can tolerate larger amounts than in possibly any other disease, except in the anemias. The following are preparations of arsenic chiefly used:

1. Liquor potassii arsenitis, Fowler's solution, in doses of 5 to 25 drops in water two or three times daily. Norton, at Cleveland, Georgia, gave a pellagrin 30 drops three times daily without untoward symptoms. The dose can be increased and decreased in the graduated way, and a watch kept for the signs of saturation, such as puffy lids, swollen face, peculiar breath, and abdominal griping.

2. In addition to the use of Fowler's solution by mouth, it is well, in order to give the largest amount of arsenic with the least danger and inconvenience, to administer hypodermatically one of the newer preparations. Of these sodium cacodylate, soamin, or atoxyl are to be preferred. Cacodylate of soda is probably less toxic than the others, the contained arsenic is liberated into the body slowly, and the maximum amount of arsenic is given with the minimum of toxic action. It is furnished in liquid form in ampules containing 1 cubic centimeter of the solution, with either ¾

grain or 3 grains (0.05 or 0.195 grams) of the salt, though a dose of 5 or 6 grains can be given at intervals of two to six days in many cases with perfect safety.

3. Atoxyl is the trade name of sodium arsanilate, and contains about 26 percent of arsenic. It is a white powder, readily soluble in water, and is furnished either in tablets or in ampules. It is given in doses of 3 grains, though often a pellagrin can take 5-grain doses without untoward symptoms. It is given, like the cacodylate and soamin, in intramuscular injections and under strict antiseptic precautions.

4. Soamin is the trade name of sodium arsanilate, and contains about 22 percent arsenic. It is furnished in tablets for hypodermic use, and is given in doses of from 1 to 5 grains (0.06 to .32 grams).

There is probably not a great deal of difference in the therapeutic value of these last three preparations. They are all given hypodermatically, either subcutaneously or directly into the muscles, preferably the latter. One objection raised against them is that they should be given over long periods of time, but this very fact is of safety to the pellagrin, because it keeps his system under the influence of maximum amounts of arsenic. A point in favor of the cacodylate of soda is that large doses of this can be given with perfect safety. Elrod, of Forsyth, Georgia, has treated many cases with this preparation, and given as much as 5 grains a day for five days in succession with no ill effects whatever. On the other hand, the patients showed marked improvement, with gain in weight and increased appetite.

Always strict antiseptic precautions are to be used. Lowered resistance of the pellagrin permits an easy entrance to infection, and all the more care should therefore be taken. Probably the easiest and safest way is to use a sterile needle and sterilize the area of administration on the skin with alcohol. This is the ordinary method in the hospitals, and with these arsenical preparations I have never seen infections follow.

The chief point in the treatment of pellagra with arsenic is to give as large doses as possible compatible with the safety of the patient. I have noticed in my own cases the large amount of Fowler's solution that they were able to take without any deleterious effect. Since the cause of pellagra is uncertain, the exact nature of the action of arsenic in this disease is unknown. It is certain that it is the one drug which seems to have a direct antag-

onistic action on the disease. As shown by J. C. Muir, in the *Journal of Pathology and Bacteriology* (1901, page 439), arsenic causes a decided erythroblastic reaction in the marrow of the long bones, and a slighter, but distinct leukoblastic, reaction. Whatever its action on the toxins, bacteria, or protozoa which may act as the cause of the disease, it stimulates the blood-making tissues to their full power, and, by the administration of either the cacodylate, atoxyl, or soamin, large doses are permissible. Such doses are absorbed slowly, and within reason have no cumulative effect.

I have followed the following method in the administration of arsenic to pellagrins, and I owe to Dr. J. O. Elrod, of Forsyth, Georgia, the idea of the beneficial results that follow the continual use of large doses of the cacodylate. In order to give the largest amount of arsenic, it is given by mouth as Fowler's solution, beginning with 5 drops in water two or three times daily, and increasing 1 drop daily until untoward effects begin. Some patients will continue up to 20 or 25 drops at a dose, but, as a rule, they do not stand well over 15 drops three times a day. Fritz, at Inzago, gives it in these doses only twice daily, increasing gradually.

Cacodylate of soda, or one of the other preparations, is then given by hypodermatic injection, somewhat after Elrod's method. He gives 3 grains (0.20 grams) every three days for three or four doses, then every two days for three doses. This is then increased to 5-grain (0.32 grams) doses every two days until the chief symptoms have lessened or disappeared and a gain in weight has begun. By this method the pellagrin gets Fowler's solution internally, the cacodylate directly into the muscles, and in many cases a noticeable improvement begins. Babcock has used soamin and atoxyl; Martin, of Hot Springs, prefers soamin, and Williamson, of Graham, Texas, following Martin's method, gives 3 grains of soamin hypodermatically every other day, or at longer intervals up to 100 grains (6.5 grams). The eruption, stomatitis, and diarrhea may show improvement from the beginning. The appetite is increased and the patient begins to gain weight. After the recovery from the attack the administration of arsenic should be continued for an indefinite period, giving Fowler's solution from 5 to 15 drops once daily, and a hypodermic of cacodylate of soda, or one of the other preparations, from 3 to 6 grains (0.19 to 0.58 grams). I have repeatedly given these weekly injections of the cacodylate in 6-grain (0.58 grams) doses, and the patient not only had no ill effects, but pre-

sented a continued improvement. Arsenic is not to be dropped when the attack recedes; it is to be continued from one to three months after all the symptoms have disappeared, just as a physician may give mercury or potassium iodid after all the noticeable symptoms of syphilis have disappeared. The following spring, even before there are any evidences of a subsequent attack, the arsenic should be commenced and given for from two weeks to a month.

King and Crowell, of Charlotte (*Journal of the American Medical Association,* November 18, 1911), have treated 19 cases with salvarsan. They administered this by the intravenous method, giving salvarsan in doses of 0.6 gram, and to children 0.2 and 0.3 gram. In case 1 five doses were given, one dose every twenty days. The symptoms disappeared and weight was regained. All these 19 cases showed improvement, and their histories in the spring of 1912 will be watched with interest. Martin prefers salvarsan. In some cases, since salvarsan is certainly the most powerful of the arsenical preparations, improvement will follow its use, but the difficulty and danger in its administration, the special apparatus necessary, and the expense to the patient do not seem to indicate that it will ever come into such general use as the less dangerous and, so far as is known, equally efficient cacodylate, soamin, and atoxyl. J. E. Paullin, of Atlanta, used the salvarsan in 9 cases, but was disappointed in his results.

After the attack has begun to recede, or even during the attack, if emaciation and prostration are severe, it is at times beneficial to give cod liver oil in full doses, and tonics, such as iron in its various forms, strychnin, and even quinin in malarial districts. In the anemia following a pellagrous attack these may with wisdom and for convenience be combined in one capsule with the following, subject to variation:

℞	Blaud's mass	3 j (3.9 gm.)
	Quinin bisulphate	gr. xxx (1.9 gm.)
	Powdered capsicum	gr. iij (0.19 gm.)
	Strychnin sulphate	gr. j (0.064 gm.)

Misce et fiant capsulæ XXX.
Sig.: 1 t. i. d.

Sandwith, in Egypt, attached some value to tabloids of fresh bone marrow. In America this is prepared in liquid form as the elixir of bone marrow. I have been accustomed to adding small amounts of

dilute hydrochloric acid and tincture of nux vomica to this, and this prescription seems to do good in those emaciated cases in which the diarrhea continued and dyspepsia and flatulence are troublesome.

Many physicians, following out one of Lombroso's ideas, feel called upon to give the chlorides in some form on the idea that the system is deficient in them. In Italy common salt or sodium chlorid is a government monopoly, and in former days, when poverty was more prevalent in Italy than at the present time, the peasants did not use enough salt because they were simply too poor to buy it. As a matter of fact, salt is used more freely in this country than in Europe, and, so far as I have been able to discover, pellagrins in America receive as much salt as they need in their ordinary diet. Certainly, if they need more, it can best be given as common salt in the food and not in medicine.

H. P. Cole and J. G. Winthrop, of Mobile, Ala., have transfused 20 cases of pellagra, and conclude: "We may safely resort to transfusion in the severe type of cases, steadily retrogressing under approved therapeutic procedures. We have noted no advantage in the employment of a donor who has recovered from pellagra as compared with the donor who has never had pellagra. There is apparently no advantage in the use of a relative for a donor as compared with the use of a nonrelative." They show as a result of these transfusions 60 percent of recoveries. It is, of course, too early to state whether these cases were permanently cured. Bennett and Scott, of Austin, Texas, surgeons to the Austin Sanitarium, have transfused 16 cases, with recovery in 13, or 73 percent. The account of their cases appears in the *Bulletin of the Texas State Board of Health* for October, 1911. Dr. W. S. Goldsmith, of Atlanta, and I used this method in 3 cases. We noticed in each case temporary improvement. Two of the cases subsequently died, 1 is still living, but still shows signs of the disease. Operation for transfusion does not require an anesthetic, and in the majority of cases is not followed by any shock to the recipient. The operation certainly will prolong life in a number of pellagrins, but I have not been convinced that it is either generally advisable as a routine method in advanced cases, or that it results in a permanent cure of the disease. When these patients reach the degree of prostration which necessitates transfusion, it is probable that the organic changes in the brain and cord have proceeded so far that permanent improvement is hardly to be expected.

DIET.

The dietetic management of pellagra concerns diet—first, during the attack, when the stomatitis, glossitis, dyspepsia, and diarrhea are present; and secondly, diet in the intermission.

Diet During the Attack.—The pellagrin should be on as generous and as nutritious a diet as is compatible with his powers of digestion and the condition of his alimentary tract. His strength is to be conserved, and his diet is to him both a food and a stimulant. When the attack is at its height, the mouth raw and sore, solid food can not be taken. Even acid liquids—as orange juice, orange and lemon albumen, and grape juice—give pain, and are to be avoided. At this time soups or broths of the ordinary kind, milk, strained oatmeal, coffee, tea, malted milk, may be used. Sweet milk may produce indigestion, and it can be peptonized, thinned with water, or lime water added, in the judgment of the physician. This liquid diet should be given during the height of the attack every two to four hours and pressed as far as possible. Occasionally the pellagrin at this time may be nauseated, and for half a day or even a day or two be unable to take but little food, and then the mouth heals rapidly, the nausea lessens, and nourishment can be taken every two hours. It is a good rule to follow, as far as possible, the appetite, and, when the patient can and will take nourishment, to give it. Buttermilk and lactone are of service here, and in many cases are pleasant to the patient. As the attack recedes and the patient improves, a general diet may be given.

Diet Between Attacks.—As convalescence begins, the liquid diet may be changed to a light diet, with the addition of mashed Irish potatoes, mashed sweet potatoes, boiled or scrambled eggs, butter, toast, scraped beef, rice with milk, and fruits. It is well at this time to give the three ordinary meals at breakfast, dinner, and supper, and nourishment at 10:00 a. m., 3:30 p. m., and bedtime. I have found in this way, by forcing the diet, improvement is more rapid and the patient takes even more food than he thinks possible. At these intermediate times, buttermilk, sweet milk, milk shakes, orange albumen, may well be given. At bedtime a glass of milk, preferably buttermilk, aids sleep and increases nutrition.

With continued improvement, the change from the light diet to a general diet may be made, with a continuance, so far as possible, of the nourishment between meals and at bedtime. Added to

the articles already mentioned are meats, as broiled steak, roast beef, chicken, and fish. Hog meat is to be avoided. The pellagrin has lost flesh during his attack, and consequently there is a demand on the part of his system for protein containing foods. In addition to the meat, eggs can be freely given and the lighter varieties of cheese. Rice, hominy, the more easily digested vegetables—especially potatoes, English peas, Boston baked beans—are favorites at this time. There may be some difference of opinion as to the use of hominy, but I have never seen any ill effects follow its use. Butter and fats are to be given in large quantities, and, as a rule, will be found to be digested easily. The pellagrin in his tissues demands protein, carbohydrates, and fats, and his diet is to be as generous as his condition permits and as his digestion is good.

The question naturally arises, in view of the corn theory of pellagra, as to whether articles of food which contain corn are to be permitted. At the Peoria State Hospital 56 patients subsisted for one year on a carefully selected noncorn diet, and 56 patients in another group were given an excessive corn diet for a similar period. At the end of twelve months there were no developments that were in the least conclusive. A few cases of pellagra developed in each group, but, on the whole, the corn-fed patients showed fewer cases than the patients on a corn-free diet (Zeller, *Journal of American Medical Association,* November 18, 1911, page 1689). More than one hundred articles of food are manufactured from corn, and it is a staple article of diet in two hemispheres. In the present unsettled state of the profession in regard to the cause of the disease, many physicians hesitate to permit the use of corn-containing foods. In some patients I have forbidden their use and in others I have permitted it, and I have failed to see any difference in the results. Syrup is made from corn, starch is made from corn, hominy is made from corn, bread is made from corn, batter cakes are made from corn, muffins are made from corn, and in the southern states at least the majority of pellagrins, as well as the majority of nonpellagrins, eat corn in one form or another. If the physician believes corn to be the cause of pellagra, he will forbid his cases to use its products as food. If he does not believe corn to be the cause of pellagra, he will permit his cases to use its products as food. It is a matter of preference and not a matter of results.

HYGIENIC MEASURES.

Because a patient has pellagra is no reason for putting him in bed. It has been a custom in certain localities in the South to put the pellagrin in bed as a part of the routine treatment. I observed this matter very carefully in Italy, and the impression was forced on me that, as a rule, better results will be obtained if the pellagrin is kept out of bed as long as possible. He may lie down in the morning and again in the afternoon, but to stay in bed day in and day out, unless his case is already hopeless, increases his weakness and his depression. As one learned Italian physician remarked to me, "As long as we can keep the pellagra patients strong enough to stay up and out of bed, the better for them." Sandwith, in Egypt, gave his patients an airing twice a day. While it is necessary, on account of the diarrhea, the extreme weakness, or the cachexia in the advanced stages, and in the infective exhaustive types among the insane pellagrins, for them to be in bed, I am convinced that the less the other cases remain in bed the better for their physical strength, their appetite, their digestion, and their mental condition. Close, dark rooms are to be avoided. Ventilation, shade, fresh air, and reasonable exercise when possible are all desirable.

The pellagrin should have a daily bath. Extremes of heat and cold are to be avoided. Tepid water, to which has been added common salt or a lump of crude alum, is both pleasant and invigorating. I find the alum bath as suggested by Boggs in typhoid fever (*Journal of the American Medical Association,* June 25, 1910, page 2124) soothing to the skin, stimulating, and even better than the plain or salt baths. The crude lump alum may be purchased at any drug store. A small lump the size of an egg should be dissolved in a little hot water and then added to the tub of tepid water, and the bath taken as usual. The hardening influence of the alum bath on the dermatitis is pleasant, the exfoliation of the skin is hastened, and the tenderness of the elbows, knees, hips, and shoulders lessened.

Climate.—Strambio, quoted by Sambon, called attention to the improvement that sometimes follows when the pellagrin changes his place of residence. One such patient, afflicted with the chronic form of the disease, with recurrence of spring attacks and who previously lived in the country, was retained by Strambio as an

orderly in the hospital, and for three or four years the spring attack failed to recur, though there were evidences that the pellagra still remained in the system. Bass, of New Orléans, has recently called attention to the improvement in a few of his own patients after he had sent them to Denver and to Tennessee, where the altitude was higher and the climate cooler. I had a similar experience with two cases, both of whom went to the mountains. Hutchins, of Atlanta, noted a marked improvement in a case he sent from Georgia to New York state. One possible reason for the improvement of a pellagrin who comes from the country districts to the city is this change of climate, which, together with the change of food, seems temporarily at least to result in a gain of weight, increased appetite, and more cheerful outlook. Whatever the cause of pellagra, whether the disease be infectious or toxic in nature, the change of residence certainly removes the patient from the danger of reinfection and lessens the danger of more poison. Pellagra disappears in the winter, and the change to a cooler climate would certainly seem advisable when practicable. Of course, this is possible only in a few cases, and may result in temporary benefit if such a change is possible just after the attack.

TREATMENT OF SPECIAL SYMPTOMS.

Dermatosis.—The dermatitis, as a rule, needs no special treatment. The patient, during the attack with the dermatitis in full bloom, should not be exposed directly to the sun, but should remain in the shade. Neither should the patient at this time be exposed to artificial heat, as this aggravates the inflammation just as truly as does the sunlight. It is not necessary to bind the hands in bandages or cover them with cloths in order to keep out the light. The solution of iodin in oil in a 5-percent strength will hasten exfoliation when applied to the hands. As a rule, the oxid of zinc ointment is beneficial if the swelling of the skin is sufficient to cause tenderness, and as the dermatitis recedes this ointment prevents cracking and fissures, and hastens the shedding of the skin. If there is much itching, carbolic vaselin or equal parts of oxid of zinc ointment and lanolin, with a few drops of carbolic acid added, are soothing. If solutions are used instead of ointments, 1:2,000 solution of cyanide of mercury once or twice daily, normal salt water, or weak alum water are all good. This alum

water is prepared by putting a small lump of crude crystal alum into a bowl or pan of water. Its stringent effect relieves burning and itching temporarily in the hands and feet. I have found that in some patients this burning is relieved by cold applications or cold water, and in others warm water seems to do more good. The dermatitis with vesicles needs more careful treatment and attention than the ordinary form.

Diarrhea.—The diarrhea is to a degree dependent on the decrease in the hydrochloric acid, pepsin, and rennin of gastric juice. During the height of the attack, however, when the diarrhea is apt to be worse, the stomatitis and the esophagitis make the mouth and esophagus so sensitive that the acid can be given only in small quantities, if at all. At this time a prescription containing tincture of nux vomica, bismuth, and elixir of lactated pepsin is frequently of service. This may be put in the form of an emulsion. Later another prescription containing dilute hydrochloric acid may be given when the condition of the mouth and throat permits. The administration of these artificial digestants not only tends to lessen the diarrhea, but also aids digestion, favors absorption, increases the stimulation, and promotes the metabolic activity, with a gain in weight. When the diarrhea is very bad, and drains the patient to a serious degree, one should not hesitate to administer opium. Better a few hypodermics of morphin and rest than no rest and the loss of many pounds. Instead of morphin, an occasional dose of paregoric, codein, or even the deodorized tincture, may be given. On the days when the diarrhea is bad the patient should be quiet, but not neecssarily remain in bed, and the diet should be either liquid or very light.

Stomatitis.—The stomatitis and glossitis during the acme of the attack are not only very painful to the patient from sheer rawness in the mouth, but chewing, swallowing, and talking are actually interfered with. The gums are raw and tender, a tooth brush can not be used, and the mouth is not clean. A mouth wash here is of service, and the liquor antisepticus of the Pharmacopeia, or the liquor antisepticus alkalinus of the National Formulary, diluted with 1 to 3 parts of water, furnish mild and helpful alkaline mouth washes and gargles. If a physician has several pellagrins under treatment at one time, it is well to have one of the local druggists prepare a gallon or so of one of these preparations. Hydrogen dioxid, 1 part to 3 or 4 of water, or 1 ounce of chlorate of potash to

1 pint of water, are of service. In lieu of the tooth brush, absorbent cotton on tooth-picks, used with one of these solutions or with cold normal salt water, will tend to relieve the tenderness of the gums and remove particles of food from the teeth. At times the mouth is so tender that even such weak acids as orange juice, weak lemonade, or pineapple juice will give pain. When the ulceration on the tip of the tongue and lips is marked, argyrol or nitrate of silver may be used, but, as a rule, the alkaline solution will be found sufficient.

The increased flow of saliva occasionally calls for treatment. One grain of atropin to 1 ounce of water, each minim representing $\frac{1}{480}$ grain of atropin, may be administered in doses of 1 to 5 minims every two to four hours. An ice bag over the parotid gland, alternating from one side to the other, tends to relieve this condition.

Nervous System.—The nervous system of a pellagrin, especially during the attack, is on edge. Narcotics and sedatives are to be avoided when possible, and, when given for insomnia or for an outbreak of mania or hysteria, should be administered in small doses. A cold sponge bath or an actual cold bath at this time is often of more service than a drug. The ordinary bromides, or 5- to 10-grain doses of veronal, are usually sufficient.

When insanity develops, the pellagrin should be put either in a private institution which cares for such patients or in a state asylum. No home is a fit place for an insane pellagrin. When they become insane, the highest form of real service both to them and to the immediate family is to place them where they can be really cared for and prevented from doing injury either to themselves or to others. The average state institution in this country is presided over by physicians of high scientific attainment and ability. The asylums are clean, the food is good, all liberty compatible with safety and order is granted. It may be a disgrace to go insane in some few cases, but it is no disgrace for an insane person to be cared for, and the place to be cared for is in an asylum. The physician, whenever the patient is insane and strong enough to travel, should advise removal to such an institution.

Vertigo is not benefited to any degree by medicine. When it is severe, rest in bed, quiet, and slowness in walking, rising, or sitting is to be advised.

CHAPTER X.

CAUSE OF PELLAGRA.

The cause of pellagra is unknown. The nature of the disease is in doubt. The pathology of the disease does not throw any light on its cause. It has been ranked alongside of many diseases. From the changes in the spinal cord it has been considered similar to syphilis and to such parasyphilitic diseases as locomotor ataxia and paresis. It has been compared to scurvy in that it was supposed to be due to errors in diet and poison in the food. It has been compared to leprosy, both on account of the involvement of the skin and on account of its power to produce cachexia and weakness. It has been assumed by many that pellagra is not a disease; that the syndrome of symptoms called pellagra does not constitute a distinct malady, but that these various symptoms belong to other maladies, such as errors in the metabolism, diseases of the alimentary tract, primary degeneration of the spinal cord, the effects of bad heredity, and unknown conditions and processes. Pellagra is a disease whose cause is unknown.

Two facts of a negative character are prominent in its history: (1) probably as many different causes have been assumed as there have been remedies given to cure it; (2) these causes, as numerous as they are, have been only assumed, and not one of them has been proved in a scientific manner.

If we knew no more the cause of malaria than we do at present of the cause of pellagra, we certainly would be ignorant of the cause of the former. A theory is one thing and its proof is quite another thing. What is needed most in pellagra is the proof of a cause. It is true that we are not lacking in theories, but it is also true that the causes thus far advanced are only theories, and they have only been advanced. Each of them must forever remain in the domain of theory until one or all of them are shown to be incorrect, or until one of them, or a new theory, is shown to be a

true theory. It is not an opinion, but a proof, that gives us the cause of a disease. It may be possible that one of the many theories of pellagra may some day be proved. It may also be possible that not one of all the theories thus far advanced is correct, and a new true theory may come in, whose proof at one fell swoop will transform our present-day theories into memories.

Among the causes that have been assigned for the disease is, first and foremost, Zea mais, maize, or Indian corn. It has been assumed to be due to bad nourishment, or poor food of whatever character. It has been assumed that any cereal, if given too long or damaged sufficiently, might cause the disease. It has been assumed that too little salt is a cause, and, again, that too little alcohol in the form of wine may cause it, and in Spain many physicians thought that too much alcoholism was the cause. The first great cause of pellagra was considered to be the sun, then poverty, and the recurring answer has been that poverty and the sun are everywhere. As Procopiu well says, "the sun is not an appendix to any one country." Along with malaria, its cause has been assigned to an unknown miasma, as unscientific as its nature is unknown. Billod believed that mania was the cause. Schelling believed that pellagra was more frequent in the presence of marshes and wet places.

Against this theory of corn is the recent idea advanced by Sambon that it is an infectious disease caused by the presence of a parasite, either protozoan or bacterial, in the human body; and that this organism, whatever its character, is probably conveyed by an insect of some kind. In a broader way, these two theories may be expressed as follows:

1. Pellagra is an intoxication.
2. Pellagra is an infectious disease.

The evidence and arguments for each of these theories will be given in detail.

IS PELLAGRA AN INTOXICATION?

For more than a hundred years, in an untold number of articles and in books whose authors have devoted much study to the problem of pellagra, Zea mais or corn has been held to be in some way the cause of the disease. Two schools have arisen—one, represented chiefly by the Italians, the French physicians, and the physi-

sians of Austria, believe that in some way pellagra is an intoxication caused by poisons contained in Indian corn, and those holding this belief are called Zeists; another group, represented chiefly by physicians in Spain, by Sambon and his followers, and by occasional physicians in the three countries above mentioned, do not believe corn to be the cause of the disease, and are therefore called anti-Zeists. Marzari, in 1810, stated the positive view that corn was the only cause of the disease, and on this proposition the discussion and the difference of opinion has continued. Suffice it to say that after a hundred years of research, of study, and of experience with the disease, the Zeists still differ among themselves as to just how corn does act as a cause, and, in the language of one of their number, "with the accumulated evidence of a hundred years they still assume, but do not prove, that corn is in some way the cause." If corn is the cause, more concentrated evidence must be brought forward before the corn theory meets wider acceptance.

The history of Indian corn is given fully in Bailey's Encyclopedia of Agriculture and in the Encyclopedia Britannica. It seems to have originated in South America, and to have been carried to Spain by the Spanish soon after the discovery of the American continent. There are seven varieties of corn commonly known:

1. Zea mais tunicata, or pod corn. Each kernel is inclosed in a husk. Grown in Brazil.

2. Zea mais everta, or pop corn. The grain has a large proportion of endosperm. Ear and grain both small.

3. Zea mais indurata, or flint corn. Endosperm starchy and inclosed in a horny layer. Color of grain white, yellow, red, or mottled. Cultivated in Canada and northern United States.

4. Zea mais indentata, dent or field corn. Starchy endosperm extending to summit of grain, inclosed in horny endosperm. The starchy matter is indented after drying and shrinking. This is the corn commonly grown and eaten in the United States. It is a low variety.

5. Zea mais amylacea, or soft corn. White, red, or yellow, lacks a horny endosperm, with a uniform shrinkage of the grain. Formerly cultivated by the Indians in North and South America. Grown in Europe.

6. Zea mais saccharata, or sweet corn. Garden corn, used as a vegetable and as canned sweet corn.

7. Zea mais, precocious and small. The ancient form in Peru, and found in the graves of the ancient Peruvians.

ANALYSIS OF INDIAN CORN.

The following is an analysis of Indian corn according to Bulletin 298, "Food Value of Corn and Corn Products," by Charles D. Woods, D. S. C., United States Department of Agriculture:

TABLE 1.—COMPOSITION OF DIFFERENT PORTIONS OF A GRAIN OF CORN.

Portion of corn kernel.	Proportion in original grain.	Water.	In water-free material.				
			Protein.	Fat.	Carbohydrates.		Mineral matters.
					Starch, sugar, etc.	Crude fiber.	
	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.
Whole kernel ..	100.0	24.7	12.7	4.3	79.3	2.0	1.7
Skin	5.6	15.3	6.6	1.6	74.1	16.4	1.3
Germ	10.2	29.6	21.7	29.6	44.7	2.9	1.1
Endosperm	84.2	24.7	12.2	1.5	85.0	.6	.7

TABLE 2.—AVERAGE COMPOSITION OF CEREAL GRAINS.

Kind of cereal.	Water.	Protein.	Fat.	Total carbohydrates.		Mineral matters.	Fuel value per pound.
				Starch, sugar, etc.	Crude fiber.		
	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.
Indian corn ...	10.8	10.0	4.3	71.7	1.7	1.5	1,800
Barley	10.9	11.0	2.3	69.5	3.8	2.5	1,735
Buckwheat	12.6	10.0	2.2	64.5	8.7	2.0	1,600
Kafir corn	12.5	10.9	2.9	70.5	1.9	1.3	1,630
Oats	11.0	11.8	5.0	59.7	9.5	3.0	1,720
Rice	12.0	8.0	2.0	76.0	1.0	1.0	1,720
Rye	10.5	12.2	1.5	71.8	2.1	1.9	1,740
Wheat	10.6	12.2	1.7	71.3	2.4	1.8	1,750

It will be noted from table 1 that nearly one-third of the germ is fat, and from table 2 that 4.3 percent of Indian corn is fat.

TABLE 3.—AVERAGE COMPOSITION OF CORN PRODUCTS AND WHEAT FLOUR.

Kind of material.	Water.	Protein.	Fat.	Carbohydrates.		Mineral matters.	Fuel value per pound.
				Starch, sugar, etc.	Crude fiber.		
	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.
Corn, whole grain, average	10.8	10.0	4.3	71.7	1.7	1.5	1,795
Corn with low protein content	10.5	6.0	3.8	78.5	78.5	1.2	1,685
Corn with high protein content	10.5	12.9	4.4	70.8	70.8	1.4	1,695
Corn, white	11.4	10.8	5.0	68.8	2.5	1.5	1,690
Corn, yellow	11.9	10.7	4.8	68.9	2.2	1.5	1,690
Sweet corn (matured)	8.8	11.6	8.1	66.8	2.8	1.9	1,750
Pop corn	10.7	11.2	5.2	69.6	1.8	1.5	1,710
Hominy, fine	11.0	9.4	.7	78.2	.4	.3	1,810
Samp, coarse	10.8	8.3	.5	79.4	.7	.3	1,770
Corn meal (whole grain ground), unbolted	12.0	8.7	4.7	71.1	2.2	1.3	1,850
Corn meal (whole grain ground), bolted	12.0	8.9	4.9	72.0	1.2	1.0	1,765
Corn meal, granulated	12.5	9.2	1.9	74.4	1.0	1.0	1,770
Corn flour—i. e., finely ground and bolted corn	12.6	7.1	1.3	77.5	.9	.6	1,645
Corn starch	.....	.....	.....	90.0	.....	.....	1,675
Liquid glucose (for table use)	16.0	.....	.....	83.5	.....	.5	1,120
Corn oil	.....	.....	100.0	.....	.....	.....	4,040
Wheat flour	11.1	11.4	1.3	75.5	.1	.6	1,770

Summing up the general composition with an average from all varieties, it may be stated that corn contains about 10 percent of water, 10 percent of protein, 4.5 percent of fat, and about 75 percent of carbohydrates and 1.5 percent of mineral matters. All of the five classes of foods are represented in corn—its fuel value is exceedingly high, and hence its wide use as food both for men and animals.

TABLE 4.—COMPOSITION OF COOKED CORN PREPARATIONS, CORN MEAL, AND WHEAT BREAD.

Kind of material.	Water.	Protein.	Fat.	Carbohydrates.		Mineral matters.	Fuel value per pound.
				Starch, sugar, etc.	Crude fiber.		
	Percent	Percent.	Percent.	Percent.	Percent.	Percent.	Percent.
Hominy, boiled ..	79.3	2.2	0.2	17.8	17.8	0.5	380
Hoecake	52.8	4.0	.6	40.0	0.2	2.4	885
Johnnycake	29.4	7.8	2.2	57.5	.2	2.9	1,385
Boston brown bread	43.9	6.3	2.1	45.7	.1	1.9	1,110
Corn breakfast foods, flaked, partially cooked at factory	10.3	9.6	1.1	77.9	.4	.7	1,680
Corn breakfast foods, flaked and parched (ready to eat)	7.3	10.1	1.8	77.2	1.2	2.4	1,735
Indian pudding ..	60.7	5.5	4.8	27.5	27.5	1.5	815
Cornstarch blanc-mange (made with cornstarch and water) ...	87.3	2.9	.1	9.5	.....	.2	230
Parched corn	5.2	11.5	8.4	72.3	72.3	2.6	1,915
Popped corn	4.3	10.7	5.0	77.3	1.4	1.3	1,880
Hulled corn	74.1	2.3	.9	22.2	22.2	.5	490
Granulated corn meal	12.5	9.2	1.9	74.4	1.0	1.0	1,655
Wheat bread	35.3	9.2	1.3	52.6	.5	1.1	1,205

Figs. 65, 66, and 67 show a field of Italian corn and Figs. 68 and 69 show Italian corn in the ear. Fig. 75 shows a field of American corn. The corn in Italy is planted in rows two feet apart. The ground is not prepared as well, nor is the crop cultivated as thoroughly, as in America. On the Lombardian plains two crops are planted. The first, or chief, crop matures in September, and the second, or smaller, in October. The first crop in Italy averages about one ear to the stalk, and these ears are about two-thirds the length of the average American ear. The second crop would be called very poor corn in America, and the ear of this crop is about half the size of an ear of the first crop—about the size of what is

usually called in America "nubbins." The Italian corn is practically, without exception, yellow or red grains, while the American and African corn is chiefly white grains. The Italians raise poor corn as compared with the American and African standards.

The corn in Italy is gathered in September and October, and is at once shucked and shelled. The whole family seat themselves around the corn pile and proceed to shell the grains. It is then spread out on a clean, well-swept dirt surface, and allowed to dry all day in the hot Italian sun. The seed corn is hung up in ears,

Fig. 65.—Field of Italian corn, first crop; September, 1911. One ear on each stalk. Mulberry trees in background. Province of Milan, September, 1911. (Photograph by the author.)

and the remainder, to be used and ground for food and for other purposes, is swept aside as shown in Fig. 71. The two reasons for the failure of the Italians to grow good corn are, first, their poor methods of cultivation; and, second, the close proximity of the mountains renders the nights too cool for the crop to reach the size and growth possible in America and Africa.

Owing to the color of the corn grains, the corn meal of Italy is usually light-yellow in color. It is prepared in soft form (the

American corn meal mush) by mixing it with water and perhaps a little grease or fat, putting it in a pot, hung in the old-fashioned way from the chimney over the fire, and cooked for hours, stirred at intervals to prevent burning. It is then eaten somewhat after the order of the American hominy, or prepared in the form of a cake or pattie by frying or baking. This preparation is known in France as gaude, in Italy as polenta, and in Roumania as malaliga. Salt is used in mixing, or, before cooking, the dry meal is made up with salt water. The corn meal in Italy is often mixed with an

Fig. 66.—Field of Italian corn, first crop; September, 1911. One ear on each stalk. Province of Milan. (Photograph by the author.)

equal amount of wheat flour, and the whole baked in a cake a foot in diameter and cooked until it is hard and dry. This corn bread in Italy is known as pane giallo, or yellow bread.

The different theories at present which consider corn to be the cause of the disease are, with one exception, built around the single proposition that corn spoils. It is useless to discuss in detail the numerous theories that have been advanced in the past hundred years in an attempt to show the change from good corn to spoiled

corn, and the ingredients and poisons in spoiled corn which cause the disease. The following are the chief theories advanced:

1. Good Corn Causes Pellagra.

(a) Marzari in 1810 first advanced the theory that corn, and especially the poorer qualities, lacked sufficient albuminous material

Fig. 67.—Field of Italian corn, second crop; September, 1911. One small ear or "nubbin" on each low stalk. Province of Milan. (Photograph by the author.)

to be a good food, particularly a food on which people depended as largely as did the peasants of Italy at that time. Another phase of this same idea was advanced by the elder Strambio, who considered corn to lack a sufficient supply of nitrogen.

(b) During the early part of the nineteenth century the more radical of the Zeists believed good corn to always contain a poison or a toxin of some kind, and that different people varied in their susceptibility to this poison. In this way was explained the fact

that, while every one in a community might eat corn, only those who were most susceptible to this poison developed pellagra.

(c) Toward the close of the nineteenth century the idea was advanced by Neusser that good corn during digestion in the intestines elaborated a poison which caused the disease. Later De Giaxa advanced the idea that the elaboration of this poison from

Fig. 68.—Ear of Italian corn, first crop; red grains. (Photograph by the author.)

good corn during digestion was due to the activity of the colon bacilli in the bowel.

At the present time these three explanations of the corn theory are no longer held even by the more radical of the Zeists. Each phase of the proposition that good corn causes the disease is held to be unreasonable, and at variance with the universally accepted fact that good corn is one of the best and most nourishing articles of human diet. The seekers after an explanation as to just how

corn does act or what it is in corn that acts as the cause turn to the proposition that

2. Spoiled Corn is the Cause of Pellagra.

This proposition is, in turn, explained in three different ways by three different schools of Zeists.

(a) Various fungi found on spoiled corn are themselves poisonous, and, when such corn is eaten, pellagra results. The pivotal point here is that the fungi poison the body, and are the cause of the disease and not the corn itself. Chief among these fungi which have been incriminated are penicillium glaucum, the common blue mold as seen on molded bread (Fig. 81); mucor racemosus and

Fig. 69.—Ends of three ears of Italian corn; first crop; red grains. (Photograph by the author.)

the species of aspergillus known as the green mold; species of the saccharomycetes or yeast fungi; oöspora verticilloides; and ustilago maydis, which causes the well-known corn smut. Spoiled corn is thus infected by these various fungi, and, when such corn is eaten, unknown poisons in the fungi cause pellagra. This idea is weakened by the fact that these different fungi can hardly all act as the cause of a disease, and yet each of them has its supporter among the research students of pellagra.

(b) Various bacteria growing on spoiled corn are themselves poisonous, and, when such corn is eaten, pellagra results. The chief bacillus which has been incriminated both by Majocchi and Cuboni, and called by them the bacillus maidis, is now known to be

the common potato bacillus or bacillus solanacearum, the toxic effects of which are in no way similar to pellagra. Carrarioli, in 1896, claimed to have found a bacillus in the blood, saliva, and stools of pellagrins, which he named the bacillus pellagræ, and which he claimed to be the cause of the disease. He has had no support. Other bacteria have been put forward as the cause, but no evidence has been advanced sufficient to prove any one of them.

(c) The fungi, chiefly the molds, cause corn to spoil, especially in the presence of prolonged dampness and darkness to which corn

Fig. 70.—Method of drying shelled corn in Italy. Corn spread out on the ground in front of the thatched one-room structure, drying all day in the hot Italian sun. Building an example of one kind in which crop is stored. (Photograph by the author.)

is subjected during shipment and in storage. The action of these fungi on the corn not only causes it to spoil, but permits the formation of poisons within the corn itself. These poisons which arise within the grain of spoiled corn are chemical in nature, and are the cause of pellagra. This represents to a large degree the idea of Lombroso, and this phase of the corn theory is called Lombroso's theory, or the toxico-chemical or the toxico-infective theory of pellagra.

Lombroso and others extracted from spoiled corn an oil of a yellowish or reddish color, known as the red oil of spoiled corn;

and a solid substance yellow in color, alkaloidal in nature, called pellagrosine, or the toxic substance of spoiled corn; and lastly, a resinous mass known as the resin of spoiled corn. Lombroso made a mixture which contained all three of these substances and which he called the tincture of spoiled corn. Lombroso and his followers claim that when either damaged corn containing the three substances or the tincture of spoiled corn is given to chickens, cats, dogs, and guinea pigs, the feathers and hair respectively fall out,

Fig. 71.—Corn swept into another kind of building after drying in the sun. This is a better building than the one shown in Fig. 70. (Photograph by the author.)

and there is a gradual development of cachexia, emaciation, diarrhea, and death. These symptoms are believed by them to be the symptoms of pellagra and that the affection in animals so fed is the same entity as pellagra in man.

At the present time the majority of Zeists lay more stress on the researches of Lombroso and on the idea that the bacteria and fungi cause poisons to be produced in the corn rather than the older view that fungi and bacteria are themselves poisonous.

The following propositions are in support of the corn theory:

1. Pellagra occurs in those countries where corn is cultivated and

eaten as food, as illustrated by Italy and the United States, where corn products are in universal use as food, in contrast with England, where corn is neither cultivated nor eaten to any degree, and pellagra does not exist.

2. The disease followed the introduction of corn into Spain. In 1840 corn was introduced into Egypt, and Pruner reported the first

Fig. 72.—Cakes of yellow polenta. Italy, October, 1911. These cakes are made of yellow corn-meal and fried in grease. (Photograph by the author.)

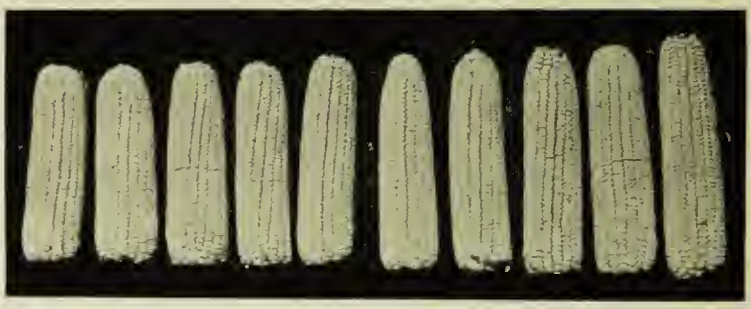


Fig. 73.—American corn from Georgia, flint variety; keeps well. (Courtesy of Professor Fain, College of Agriculture, Athens, Ga.)

case of pellagra in 1847 in that country. The prevalence of the idea that prophylactic measures taken against the use of poor and damaged corn will prevent pellagra and cause it to decrease in extent.

3. Damaged corn given to chickens, dogs, and guinea pigs causes the feathers and hair respectively to fall out, a gradual development of cachexia, emaciation, diarrhea, and death. This disease

in these animals is considered by the experimenters to be the same entity as pellagra in man.

4. The changes in the spinal cord in pellagra are similar to those which take place in ergotism, a disease due to a fungus growing on rye.

5. Pellagra occurs only in people who eat corn or its products, and does not occur in individuals who abstain from corn or its products.

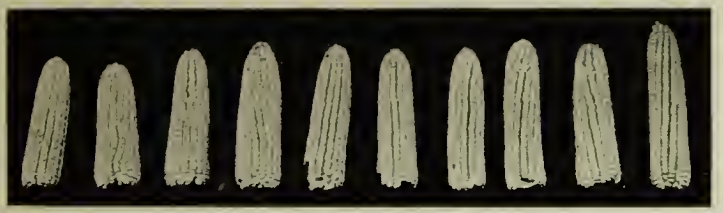


Fig. 74.—Ears of American corn from Georgia, which do not keep well; spoil easily. (Courtesy of Professor Fain, College of Agriculture, Athens, Ga.)

Fig. 75.—Field of American corn, Georgia; two to four ears on a stalk. (Courtesy of Professor Fain, College of Agriculture, Athens, Ga.)

6. The weight of opinion in Italy, Austria-Hungary, and in other regions where pellagra exists is in favor of the view that corn is the cause.

7. Pellagra is not characterized by either high persistent or periodic fever, such as occur in syphilis, tuberculosis, and malaria, and is therefore more apt to be an intoxication than an infection.

Objections to the Corn Theory.

1. There is no agreement among the Zeists as to just what substances or in just what way corn acts as a cause of the disease.

2. A poison is not apt to cause recurring seasonal attacks long after the patient has ceased to take it in his food. After a poison is removed, it does not remain in the system permanently, nor do its effects recur periodically.

3. Corn does not explain why pellagra occurs among rural popu-

Fig. 76.—One method of gathering and drying corn in America. (Courtesy of Professor Fain, College of Agriculture, Athens, Ga.)

Fig. 77.—Rail pens without covers, sometimes used for storing unshucked corn in America. Corn on the ear. (After Hartley, Farmers' Bulletin 313, United States Department of Agriculture.)

lations and is practically absent from cities. Why should the same corn cause pellagra in the country and not in the city?

4. The numerous prophylactic measures—such as the inspection of corn, the drying of corn, the maturing of corn—have had no effect on lessening the prevalence and the severity of the disease, as illustrated by Spain, where practically no preventive measures have been taken and where the disease is nearing extinction due to unknown factors, and contrasted with Italy, where many preventive measures have been taken and where the disease still exists over wide areas.

5. The topographical relations of the disease to streams and the persistency of its endemic areas are not explained by the corn theory.

6. The disease occurs in persons who do not eat corn or who have eaten it but rarely. The attacks of pellagra continue to recur in a pellagrin longer after he has ceased to eat corn.

Fig. 78.—Cribs used for drying corn in the United States. Crib shown is 240 feet long, divided into bins 6 x 8 feet to facilitate drying of the corn. (After Hartley, Farmers' Bulletin 313, United States Department of Agriculture.)

7. It is true that fungi cause such diseases as ringworm, actinomycosis, and the various mycetoma, but none of these resemble pellagra. This is evidence against the fungus theory of the disease.

IS PELLAGRA AN INFECTIOUS DISEASE?

A broad view of infection is given by Professor Ritchie in his article on the pathology of infection in Allbutt and Rolleston's "System of Medicine:"

The study of infection in its widest and most scientific sense is almost coterminous with the study of the effect of any foreign living agent when it gains a foothold, and especially when it multiplies in the animal body. Another great truth has also emerged in modern times in the recognition of the fact that, notwithstanding the variety of clinical types produced by different agents, there is a great unity in the morbid processes set up. We must, therefore, in taking a broad view of the subject, be prepared to account for observed facts and to recognize common processes in such varied conditions as the following:

1. The action of parasitic fungi and bacteria in such diseases as favus, septicemia, tuberculosis, diphtheria, enteric fever, etc.

2. The action of parasitic protozoa in such disease as malaria, tsetse-fly disease, etc.

3. The action of what for the present are called "ultramicroscopic" living agents in such diseases as pleuropneumonia and foot-and-mouth disease in cattle, and probably yellow fever in man.

4. The action of parasites of unknown character, though probably belonging to one or the other of the last three groups, which are in all likelihood associated with such disease as smallpox, scarlet fever, hydrophobia, measles, etc.

5. It is a question whether certain phenomena associated with the presence of parasitic worms in the body ought not properly to be classed along with the phenomena of undoubted infections.

These five propositions refer to the cause of that great group known in modern medicine as infectious diseases, and, if pellagra belongs to this group, its cause must come under one of these con-

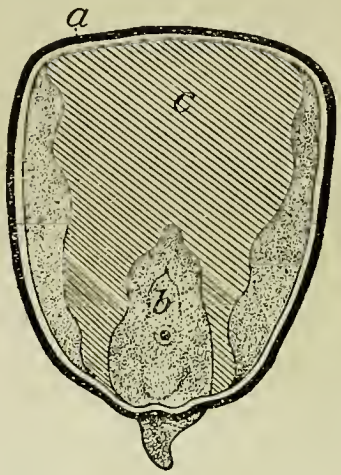


Fig. 79.—Diagrammatic section of a grain of corn. *a*, skin; *b*, germ; *c*, endosperm. (After Woods, Farmers' Bulletin 298, United States Department of Agriculture.)

ditions of infection. The body of the pellagrin must, therefore, contain either living parasitic bacteria or fungi, which are the specific causes of pellagra and of no other disease; or the pellagrin contain within his body parasitic protozoa or ultramicroscopic living agents or parasites of unknown character, causing diseases transmissible by contact; or, lastly, the body of the pellagrin must contain worms which act as specific cause of the disease. Now, it is necessary that the evidence which goes to show that pellagra is an infectious disease be presented in two ways: First, are the morbid processes carried on in the body of the pellagrin similar, in the widest sense, to the morbid processes characteristic of other known

infectious diseases, such as syphilis, malaria, sleeping sickness, hookworm disease, tuberculosis? This is the evidence from within the body, and may be called the pathological evidence of infection. Second, the evidence afforded from without the pellagrin, such as his relation to his environment, climate, temperature, home, standing and running water, age, sex, occupation, and the history of the disease in one country for a long period of time. This may be called the relational or ecological evidence of infection. The discovery of the protozoan or bacterium which causes this disease is necessary before any absolute scientific proof can be given.

(a) The Pathological Evidence That Pellagra is an Infectious Disease.

1. There is a relative increase of the lymphocytes. Other protozoan diseases—as syphilis, kala azar—show a similar increase in these cells. Trypanosomiasis, or sleeping sickness, has a lymphatic infiltration of the brain with the mononuclear cells.

2. Pellagra shows a marked increase in the lymphocytes of the cerebrospinal fluid.

3. Pellagra shows at certain stages a marked leukocytosis, similar to the lukocytosis in malaria, which is a protozoan disease.

4. Pellagra, syphilis, kala azar, malaria, and sleeping sickness are all alike benefited by arsenic.

5. The nervous system is involved centrally as in syphilis, kala azar, and trypanosomiasis. These show an affinity for the spinal cord. Leprosy, an affinity for the peripheral nerves, and pellagra, like leprosy, has peripheral nerve formications, burning, numbness, pain.

6. Pellagra, like malaria, shows a complete absence of eosinophilia. In pellagra as many as a thousand leukocytes may often be counted without the occurrence of a single eosinophile cell.

7. Diarrhea is a characteristic of infective diseases, rather than a chronic intoxication, as illustrated by cholera and the choleraic or the algid form of malarial fever as contrasted with the constipation of chronic alcoholism or beriberi.

8. Like hookworm disease, pellagra produces eye changes and often causes the formation of cataracts. These cataracts are probably due in hookworm disease to toxins elaborated by the worms and circulating in the blood and lymph for long periods. An infection may exist in pellagra with a similar elaboration of toxins.

(b) Ecological Evidence of Infection.

1. Pellagra occurs in tropical and subtropical climates where infective diseases, and especially diseases caused by parasitic protozoa and parasitic worms, are prevalent. Wherever pellagra occurs, malaria and hookworm disease are to be found, and nearly always amebic dysentery.

2. Pellagra is not characteristic of climate in the northern sections of the world, where the winter seasons are extremely long.

3. Pellagra is a rural disease, and develops on farms and in homes whose environment is rural. It is not a city disease.

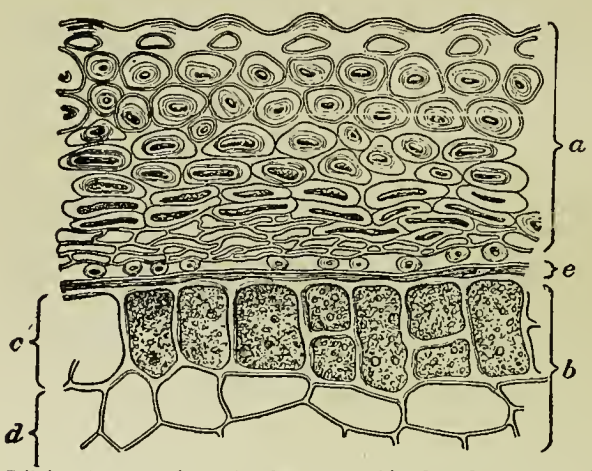


Fig. 80.—Cellular structure of a grain of corn. *a*, skin; *b*, endosperm, consisting of (*c*) aleurone cells and (*d*) starch cells; *e*, membrane.

4. Pellagra is more common in females than in males, and especially is this true in America. Both eat the same food, and a food poison affects both sexes equally. There is a reason for the predominance of female pellagrins, due in all probability to the fact that they are more exposed to the infecting agent.

5. Children six months of age develop the disease in country districts. It seems more reasonable to believe the development of the chronic disease in an infant of this age to be due to an infection arising from without than to poison in ordinary food given it infrequently and in very small quantities.

6. Pellagra bears a direct relation to the seasons in all countries where it exists. This is characteristic of infective protozoa and dis-

eases like malaria, and is probably due to the more or less fixed life span of the parasite. Intoxications are not seasonal in their relations.

7. Parasites, especially protozoa, are active in the spring, summer, and autumn, and inactive in the winter. Pellagra is active in the spring, summer, and autumn, and latent in the winter.

8. Infective diseases are widespread over the earth, as illustrated by such widespread diseases as tuberculosis, malaria, and syphilis. If pellagra is not an infectious disease, it is the only disease due

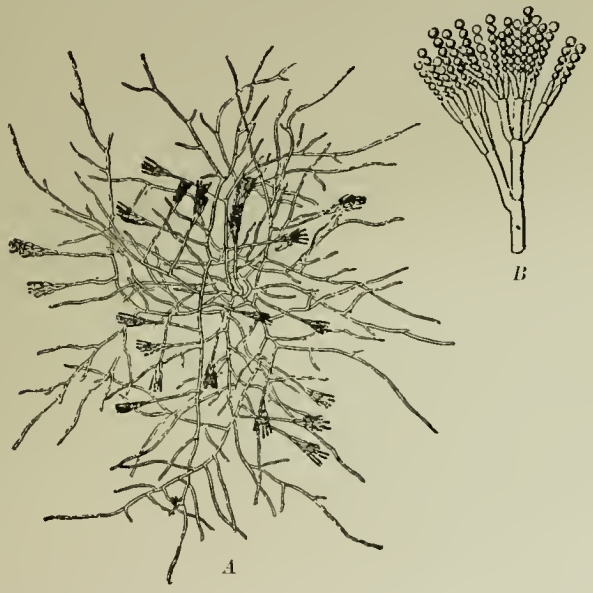


Fig. 81.—Penicillium, a common mold found on corn. *A*, mycelium, with numerous branching sporophores bearing conidia; *B*, apex of a sporophore enlarged, showing branching and chains of conidia. (Coulter, after Brefeld.)

to the ingestion of a poison formed in a grain that has so wide a distribution on the earth, is so chronic in its nature, and so persistent in its endemic relations.

9. Infectious diseases are epidemic in character—as cholera, and endemic in character—as malaria. Pellagra is epidemic, as illustrated by its recent invasion of America. It is endemic in character, as illustrated by the fact that it exists in one mountain valley for a hundred years.

Dr. Louis W. Sambon, an Italian physician, who lived formerly in the city of Milan, graduated in medicine at Naples and later

moved to London, where he is the present lecturer in the London School of Tropical Medicine, first advanced the theory that pellagra is an insect-borne disease similar to sleeping sickness, malaria, and yellow fever. The evidence of this fact chiefly relates to the topographical relations of pellagra.

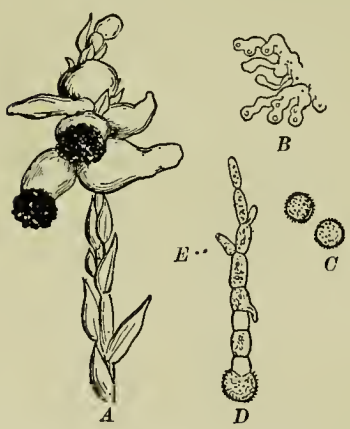


Fig. 82.—Usailago maydis, a fungus that causes corn smut. *A*, staminate flowers of Indian corn, attacked by "smut"; *B*, mycelium, showing the beginning of spore formation; *C*, ripe spore (X600); *D*, germinating spore, developing a promycelium, with sporidia, *E*. (Campbell, after Brefeld.)

Fig. 83.—The simulium fly and larva. (After Comstock.)

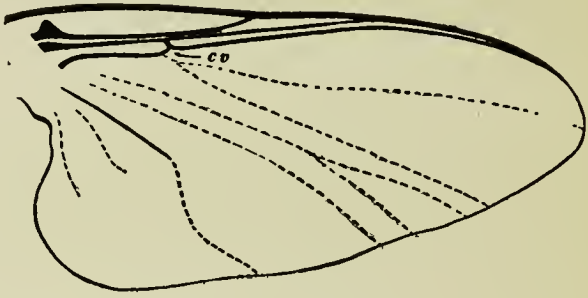


Fig. 84.—Wing of simulium fly, showing venation.

1. Pellagra is a disease of place. It occurs in restricted areas in a country where it is endemic. Sambon found numerous illustrations of this in Italy, and Lavinder, with Sambon, was "frequently impressed with the statements of practitioners in pellagrous sections that all of their cases come from this or that restricted locality."

The disease is found in an area, as a rule, at the foothills of

mountainous regions in areas traversed at frequent intervals with small streams. The vast majority of pellagrins in all the countries of the world where pellagra exists live in such areas. Now, in such areas in one of these mountain valleys many cases of the disease may originate, while no other cases may exist for miles around this valley.

One of the most remarkable facts brought forward by Sambon as a result of his researches in Italy is that these endemic centers remain the same for a century. This is evidence in favor of the view that the disease is spread by an insect. He found that the present distribution of pellagra in the province of Bulluno is the same as that observed by Xecchinelli in 1818 and Odoardi in 1776. Taking these three dates—1776, 1818, and 1910—"the disease affects the very same places along the valleys of the river Piade."

2. Pellagra originates chiefly along streams and water courses. Sambon first pointed this out in Italy, and, following his example, I have found the same condition to exist in the southern states. The following table illustrates the relations of thirty-five pellagrins in Georgia to streams:

Number.	Number of Pellagrins.	Residence.
1	3	Swamp, three streams.
2	3	Swamp.
3	1	In 50 yards of stream.
4	1	Location wet and swampy.
5	2	In ¼ mile of stream.
6	1	Unknown.
7	1	In ¼ mile of standing water.
8	1	In ¼ mile of branch.
9	1	Between two streams.
10	1	In ¼ mile of pond and stream.
11	1	In 300 yards of branch.
12	1	On Chickamauga creek.
13	1	In 220 yards of creek.
14	1	In 300 yards of creek.
15	1	In ¼ mile of creek.
16	1	On stream.
17	1	On stream.
18	1	Resided on pond 5 years.
19	1	Between two springs and fresh branches.
20	1	In 1 mile of stream.
21	1	In 250 yards of stream.

Number.	Number of Pellagrins.	Residence.
22	1	In 200 yards of stream.
23	1	12 years in 100 yards of stream.
24	1	15 years in 100 yards of stream.
25	1	In 1 mile of stream.
26	1	In ¼ mile of stream.
27	1	In 30 yards of stream.
28	1	On sea coast.
29	1	In city.
30	1	In 100 yards of stream.

Fig. 85.—Legs of a chicken showing pellagrous symptoms produced by feeding maize spoiled by inoculation with a specific bacterium. (By Dr. C. C. Bass.)

Fig. 86.—Legs of another chicken manifesting similar symptoms to those of chicken in Fig. 85. (By Dr. C. C. Bass.)

A single illustration from Sambon will suffice:

It is a well-known fact among the peasants themselves that in pellagrous districts the disease is far more prevalent and severe in those who live quite close to a stream than in those who dwell at some distance from it on the neighboring heights. At Trestina (Citta di Castello), a place I visited in the company of Professor Centonze and Dr. Sediari, two peasants, Tommaso Paronni and Emidio Caracchini, told me that some years ago they used to

live by the Torrent Nestore, but that, owing to the severity of the disease, they had been obliged to abandon their houses near the stream and take refuge with their respective families on the Trestina hill. There are places on the Nestore, on the Minimella, and on a thousand other brooks and creeks where healthy newcomers invariably contract the disease. On several occasions I have seen families all the elder members of which were pellagrins, while the two or three youngest children were not, owing to the fact that the parents had removed from a pellagrous to a healthy locality before the birth of the latter.

Fig. 87.—Bobbin Creek, near Athens, Ga., where the simulium larvæ were first found in Georgia by Professor J. M. Reade. The larvæ are abundant on the rocks, where the water is swift. (Photograph by Professor J. M. Reade.)

In July, 1911, Dr. L. B. Morse, of Hendersonville, N. C., became interested in the relation of pellagra to streams, and found in four cases in his community the disease originated while the patients were living near streams. Assistant Surgeon R. M. Green found the same conditions to exist in three counties in southwestern Kentucky, and regarding the 140 pellagrins which he found in these counties he writes as follows:

On account of the topography of the country, the most suitable locations for homes are along the streams, and consequently a large percentage of the inhabitants live along water courses. In every instance where I was able to visit the pellagrins at their homes I found them living within 500 or 600 yards from a stream. A number of them were living in houses situated literally on the banks of the streams.

Fig. 88 shows an endemic pellagrous area in Dadeville, Ala. The stream in the center flows between the houses, those on the right being 200 yards away and situated on a hill. No cases developed here. The houses to the left of the stream each contain pellagrins, which have developed while living in these houses. The family inhabiting house No. 2 moved away, and Mrs. A., who lived in the hilly portion of the town and was perfectly healthy, moved in. In a short while she developed the disease. These three homes are situated on a gentle slope just 75 yards away from the stream. One-half mile to the left a negro cabin was situated practically on the stream. A negro woman and her daughter lived here, both developed the disease, and both died. It seems that the endemic area in this community was in the valleys trenched by these two streams, and the families that lived to the right on high ground were exempt. I know of no better evidence than is afforded by this simple illustration. I am indebted to Dr. J. Clarence Johnson for it and to his assistant, Dr. John Fitts, who made the sketch.

J. O. Elrod, of Forsyth, Ga., showed me a similar endemic area in Monroe county. This endemic area was a valley in rolling middle Georgia land, trenched by an ordinary small creek. Five cases of pellagra developed in this valley—one an old man, one a man of 40, two white women, and one negro woman. Fig. 89 shows the relation of a pellagrin to a stream in the village of Cornelia, Ga. In this case the patient had lived in a house for a great number of years, and the disease originated here and here the patient died. While in Franklin, N. C., in the summer of 1910, I studied the premises and surroundings of a pellagra patient, a woman, who had recently died. The house bordered the road in front, and behind a branch of rapid mountain water ran within fifty feet of the back porch. On the right of the house was a perfect swamp, and the stream marked out a narrow mountain valley—exactly the same topographic conditions found in Italy by Sambon.

K. H. Beall (*Journal of the American Medical Association,*

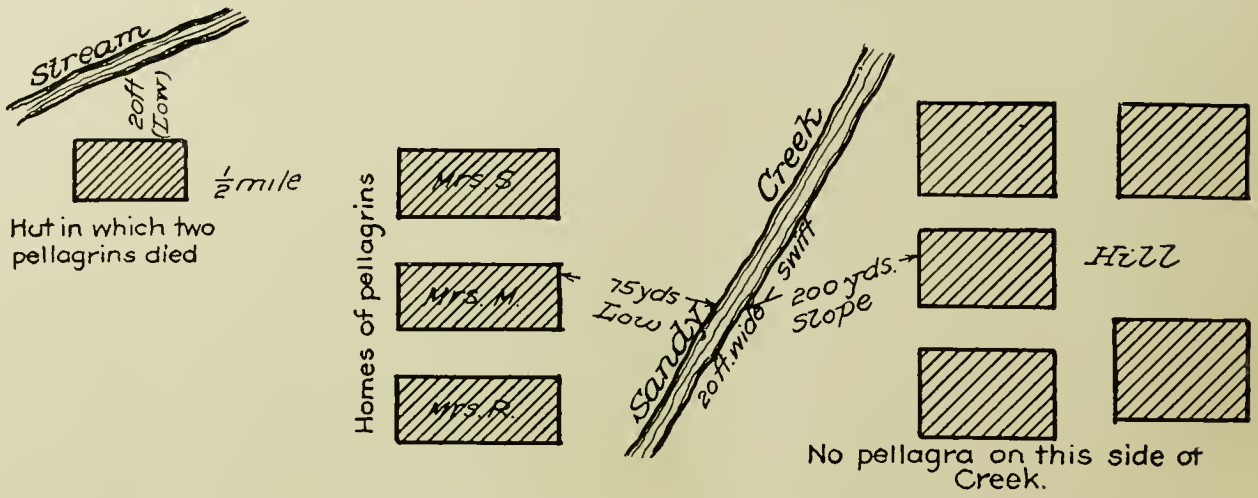


Fig. 88.—Diagram showing a pellagrous neighborhood in the town of Dadeville, Ala., and the relation of pellagra to streams. To the left of the creek seventy-five yards, on a gentle slope, are the homes of three pellagrins. Mrs. M. formerly lived in another portion of the town, and developed pellagra sometime after moving to the above location. To the right of the stream two hundred yards, and on a hill, there are no cases of the disease. To the extreme left of the diagram is represented a negro cabin, directly on a stream, in which a mother and a daughter died.

Fig. 89.—Diagram showing the relation of pellagra to streams in the town of Cornelia, Ga. Mrs. A. lived in the house twenty years. She developed pellagra in 1908 and died in 1911.

November 18, 1911) is the only author I have found who disagrees with the relations of pellagra to streams. He studied 54 cases, and found that 4 lived in one-half mile of a stream; 9 lived from one-quarter to one-half mile; 41 lived at least one mile; 2 lived eight miles; 4, ten miles; 1, twelve miles; 1, fifty miles, and 1 sixty miles from any overground collection of water—a general average of over four miles.

INSECT CARRIER.

Pellagra is not contagious, but spreads probably through the agency of its insect carrier as malaria or yellow fever are spread by insects.

Alessandrini agrees with Sambon that pellagra in Italy is endemic along the borders of the streams, though he believes the cause to be a species of nematode worms of the genus filaridæ. He advanced this theory in 1910 in opposition to the corn theory, but it has neither been proved nor has it developed followers. From the foregoing it is evident that the same conditions in by far the larger number of cases prevail in the United States. Again, pellagra is rural and not urban. I was impressed with this at the hospital for the treatment of rickets and other deformities of the city of Milan. This very charitable institution sends out over the city every morning and collects the deformed children of the poor, keeps them in the hospital all day for treatment and while their parents are working. I was told that in all their experience they had not found any of these children with pellagra, and yet their food is poor and certainly not any better than the food furnished the children in the rural districts in Egypt and Italy, where pellagra is common among children. It is evident that there is something in the country which is not in the city, and which is the cause of the disease. It is further evident that this something probably originates in or along streams, or standing water. Pellagra is not contagious, avoids the winter, develops in the spring and autumn, recurs and continues to redevelop at these same seasons. Pathological evidence affords reason for the belief that the disease is protozoan in origin. For all these reasons it is evident that pellagra is probably due to the agency of an insect of some kind. Sambon believes this insect to belong to the genus simulium. The following is a brief description of this fly:

The simulium fly is one of the order diptera, or two-winged flies; family simuliidæ, with the one genus simulium, having many species. Of these Sambon found three species in Italy—simulium reptans, ornatum, and pubescens, chiefly the last. The two chief species in America are simulium venustum, or black fly, the great biter of the northern woods; and simulium pecuarum, the southern buffalo gnat. This buffalo gnat causes the death of many mules and domestic animals. It is found along the tributaries of the Mississippi, through the state of Mississippi, possibly all of Arkansas, in Kansas, in Tennessee, Kentucky, and parts of Missouri, Illinois, and Indiana. Since 1850 this buffalo gnat has killed many thousand domestic animals. They appeared in the Mississippi valley as early as 1818, and in 1884 killed in Parrish, La., 300 head of stock in one week. They do not seem to appear every year in damaging numbers, but are always more numerous in time of flood. Sambon notes that in Italy the greatest number of pellagra cases occur in the flood and overflow years.

Two crops of the insects emerge from the streams each year—one appearing from February to April, and the other from September to December. The eggs are laid, when possible, in streams of rapid, shallow water, as in an ordinary branch or creek. Rock, leaves, and brush in the water are good places. They hatch in about eight days to a larva, passing in about four weeks into the pupa stage, and emerging in three weeks, after having spent the pupa stage in the bottom of the stream, as the mature two-winged fly or gnat.

The Cambridge Natural History, vol. 6, page 477, defines the simulium or sand fly, or buffalo gnat, as "small obese flies with humped back, rather short legs and broad wings, with short, straight antennæ, destitute of setæ; proboscis not projecting; will probably prove to be nearly cosmopolitan." In Great Britain these flies do not increase to an extent sufficient to render them seriously injurious, but their bite is very annoying. Simulium columbaezense has caused great loss among the herds on the Danube. They prefer brisk and lively streams, as in rapids above the waterfalls, but have been found in sewage water. Further information about these flies can be found in the "Proceedings of the Boston Society of Natural History," Hagen, 1880, pages 305 to 307; *American Entomologist*, Osten Sacken from Verdat, vol. 2, page 229. De Geer's Memoirs (vol. 1, page 328) says they attack large, smooth

caterpillars, sucking blood, and Verdat has found them sucking honey dew from the aphidæ. Osten Sacken (*Berliner Entomologische Zeitschrift,* bd. 37, 1892) says the males love sunshine and swarm high in the air; females remain at lower levels, and perhaps only females bite. F. M. Howlett, article on Indian Sand Flies, Congress of Medicine, Bombay, India, 1909.

Dr. J. Cheston Bradley, assistant professor of entomology, Cornell University, was bitten by a simulium fly in the hotel at Clayton, Georgia, in the summer of 1911, and later, on a tramp up the mountains, found himself attacked again. He did not develop the disease, of course, but the point is that people in the pellagrous area are bitten by the simulium fly, and yet previous to 1911 this fly had never been reported from Georgia, and until Dr. Bradley was bitten it was not even known in that section that man was subject to their attack. For the following reasons Sambon believes this insect to be the carrier of the disease:

(a) Simulium, so far as we know, appears to affect the same topographical conditions as pellagra.

(b) In its imago state it seems to present the same seasonal incidence.

(c) It is found only in rural districts, and, as a rule, does not enter towns, villages, or houses.

(d) It explains most admirably the peculiar limitation of the disease to agricultural laborers, a limitation which nothing else can explain in a satisfactory manner.

(e) It has a wide geographical distribution, which seems to cover that of pellagra, although certainly exceeding it, in the same way that the distributional area of the anophelinæ exceeds that of malaria, and the range of stegomyia calopus that of yellow fever.

(f) It is known to cause severe epizoötics in Europe and America.

(g) Other similarly minute blood-sucking diptera, such as phlebotomus papatassi and dilophus febrilis, are strongly suspected of being propagators of human diseases.

The evidence so far in favor of the simulium is circumstantial evidence. So far as is known, where pellagra exists the simulium fly exists, but there are many species of this fly, and the question arises which one of these species is, or are all of them, the insect carrier. There are five species of the simulium in the Austrian Tyrol. There are many species in America, but the evidence thus far adduced is far stronger in favor of an insect as the carrier of

the disease than it is definite in favor of the simulium as the carrier. Sambon's argument and later evidence for an insect is very reasonable. Whether it is the simulium fly or not remains a problem. As pointed out by Chilton Thorington (*Virginia Medical Semi-Monthly,* July 21, 1911), the mosquito is to be borne in mind. It is not known whether a certain species of mosquito is common to all pellagrous areas, but certainly it should be determined whether the mosquito has any relation to the disease. The members of the genus ceratopogon of the family chironomidæ include the small midges commonly known as punkies. It should be determined whether these have any relation to the disease, as they, too, are blood-sucking and man-biting flies. Finally, Beall, formerly referred to, has called attention to the fact that on account of the predominance of females in America it is reasonable to believe that they are more exposed to the disease. Of those males who developed pellagra in his series the majority of them were either under 20 or over 50, and, like the women, spent most of their time at home. The predominance of females is greater in this country than in Italy or Roumania, and Beall believes this to be due to the fact that the insect which causes the disease is one common to homes in the endemic districts and which bites during the day. If it were a night-biting insect, males and females would be equally attacked. This affords further evidence in favor of the necessity of investigating the mosquito as a probable cause, and the punkies.

Objections to the Theory that Pellagra is an Infection.

1. The failure to find in the blood, or in the tissues and body fluids, any parasites or specific bacteria.

2. The failure to reproduce the disease when the blood of a pellagrin is injected into the body of a healthy person or into monkeys.

Objections to the Theory that the Simulium is the Carrier of the Disease.

1. The failure to find in the simulium any protozoa or specific bacteria.

2. The inability so far to reproduce the disease when simulium flies are permitted to suck the blood from individuals suffering

with pellagra and to then bite monkeys, as illustrated by the work done by the State Board of Health of Kansas.

3. Lack of evidence to prove that blood-sucking flies other than those of the genus simuliidæ may not be the carrier of the disease.

At the present time further discussion of the cause of the disease is to no purpose. If we knew the cause, it could probably be stated in a sentence—certainly in a page. Pellagra is either an infection or an intoxication—it can not be both. It can not be caused by the poisons of both corn and protozoa. Mizell, of Atlanta, has advanced the theory that cotton-seed oil and other oils are the cause, but so far no evidence—either chemical, physiological, or economic—has been advanced in favor of his idea. Bass, of New Orleans, like Lombroso, has fed chickens on spoiled corn and caused changes in the epidermis of the leg (Figs. 85, 86), even as Lombroso did before him, but that this is pellagra in the chicken is hardly probable. Would a continued diet of spoiled wheat, or spoiled oats, or spoiled buckwheat not cause a similar condition?

Sambon's theory that pellagra is an infection has produced a profound impression. It is probable that the majority of physicians in Italy lean toward the corn theory. They have heard or been taught nothing else for a hundred years. It is probable that the majority of the physicians in the southern states lean away from the corn theory—certainly bear toward it the relation of the open mind. Many of them believe it to be an infectious disease, and I am inclined to this belief. The experiments now being carried on in the state of Kansas by Dr. S. J. Hunter (*Journal of the American Medical Association,* February 24, 1912), in which sand flies bite pellagrins and then are permitted to bite guinea pigs and monkeys, should bear some fruit. One of these monkeys so bitten became sick and developed fever. He was autopsied, and his nervous system is now being studied. Whether this experiment will result in anything is unknown, but it is at least along the right line.

The advocates of corn have had a hundred years, and have not made out their case. Sambon's theory is but two years old, and is being investigated. It behooves the Zeists to agree among themselves as to what it is in corn that causes the disease, and until this is done the burden of proof for the corn theory rests on them. It behooves Sambon and his followers to prove that pellagra is an infectious

disease, and to locate and name both the insect which acts as host to the parasite, if it be an insect-borne disease, and to find the protozoan or the bacterium which causes the disease. Both ideas can not be true. No theory is true which is not in accord with the facts. Until one of these two theories is proved or both disproved, the majority of physicians will bear to the question a relation of waiting. They have their opinions and are waiting for proof.

The history of pellagra in other countries for the past two centuries warrants the belief that the United States is facing a long period during which the disease will prevail and in which many thousand human beings will become its victims. Little children will yield themselves to its insinuating and mysterious grasp; strong men will become weak, and no longer able to render service as citizens; its mark will be left on the offspring of pellagrin mothers; and especially through the southern states its ravages and its memory will exist side by side in every rural community. It has already fastened itself on the spinal cord, and its poisons flow in the blood of probably as many as ten thousand human beings in the states today. American medicine has given to the race the serum for the treatment of meningitis, and has discovered the insect carrier of yellow fever. There is reason to believe American physicians will finally settle the problem of the cause of pellagra by the discovery and the proof of the toxin or the parasite which causes the disease. The corn theory is a century old and unproved—the infection theory of Sambon is new and unproved. Until the cause is definitely known, the wisdom of prophylactic measures is in doubt, and the hope of more satisfactory methods of treatment is delayed. In the language of a European physician, "pellagra has appeared in America, and no doubt in America the true cause of the disease will be discovered."

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